STUDIES ON THE SYNTHESIS OF PAPAVERINE

A Thesis

by

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GENERAL INTRODUCTION

Papaverine occurs in the unripe seed capsules of the opium poppy Papaver somniferum, L. in amounts ranging from 0.5 to 1% by weight. Many methods are known to industry for its isolation and purification. This alkaloid finds use in medicine as one of a group of spasmolytic drugs with a paralyzing action on the smooth muscles of the intestines and blood vessels. However, in common with other pharmacologically useful alkaloids derived from the opium poppy, the availability of natural papaverine is limited by the stringent international controls on the cultivation of this plant.

While several methods have been developed for the synthesis of papaverine, up to this decade, it was doubtful if they could compete economically with even the small yield extracted from natural sources. German research carried out during the last war, and brought to light in very recent B.I.O.S. reports, now indicates that synthetic papaverine may compete with, and even displace, the natural product.

It seems reasonably certain that any economically successful synthesis of papaverine must employ vanillin as a principal reactant. Although vanillin could now be obtained in almost unlimited amounts and at reasonable cost from the waste liquors of the sulfite pulping of softwoods, its production has hitherto been limited by the lack of adequate commercial uses.

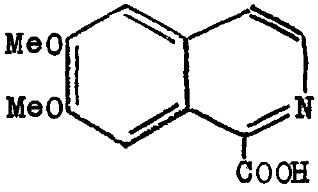
The present research had the object of exploring still further the possibility of utilizing vanillin for the synthesis of papaverine. Condensation of aminoacetal with the desoxybenzoin prepared from methylated vanillin yielded the expected Schiff base, but ring closure of the base gave only a very low yield of papaverine. The major product was a hitherto unknown isomer of the desired compound. In similar fashion, ring closure of the hydrogenated Schiff base gave an unknown isomer of dihydropapaverine.

HISTORICAL INTRODUCTION

Discovery of Papaverine and Proof of Structure

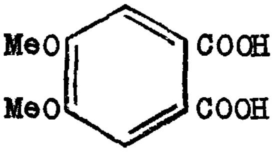
The discovery of papaverine was made in the year 1848 by G. Merck (1) who isolated it from the mother liquors of the morphine containing extracts of poppies. He analyzed the substance, its hydrochloride and platinichloride, and assigned the presently accepted formula of $C_{20}H_{21}O_4N$ to the base (2). More refined methods of separation of the alkaloid were soon evolved. Plugge (3), for example, precipitated narcotine and papaverine by adding concentrated sodium acetate to a solution of the mixed hydrochlorides of the opium alkaloids. This mixed precipitate was re-dissolved in a large volume of dilute hydrochloric acid and papaverine was precipitated with potassium ferricyanide. Collection of the precipitate and decomposition with caustic soda gave pure papaverine in amounts up to 98% of that originally present in the poppy.

Papaverine was the first of the opium alkaloids whose structure was completely known, principally owing to the efforts of Goldschmiedt (4) over the period 1885 to 1898. He showed the presence of a tertiary nitrogen atom by formation of the methiodide, and that of four methoxyl groups per mole. Oxidation of the base with potassium permanganate under varying conditions gave rise to the following compounds:



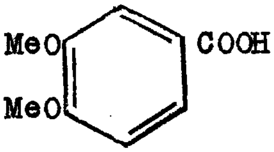
6,7-dimethoxy-
isoquinoline-1-
carboxylic acid

I



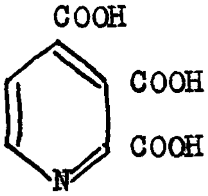
m-hemipinic acid

II



veratric acid

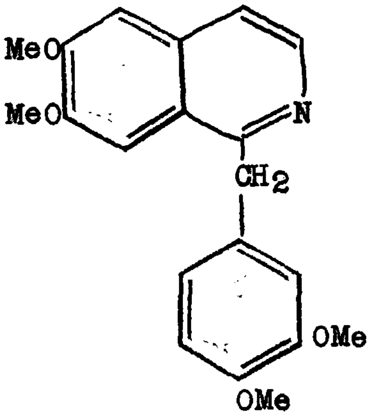
III



pyridine-2,3,4-
tricarboxylic acid

IV

On the basis of the above evidence and a mass of confirmative data which is not relevant to this discussion, the following correct structure was assigned to papaverine in the year 1888 (5):



V

Syntheses of Papaverine

Many attempts, both successful and unsuccessful, have been made to synthesize papaverine or closely related analogues. The first complete synthesis, accomplished by Pictet and Gams (6) in 1909, followed a general route for which no alternative had been discovered. All successful syntheses of the papaverine type structure involve the intramolecular condensation of an acylaminoethane derivative:

$$R\text{-}CHR'\text{-}CH_2\text{-}NH\text{-}CO\text{-}CH_2\text{-}R''$$

VI

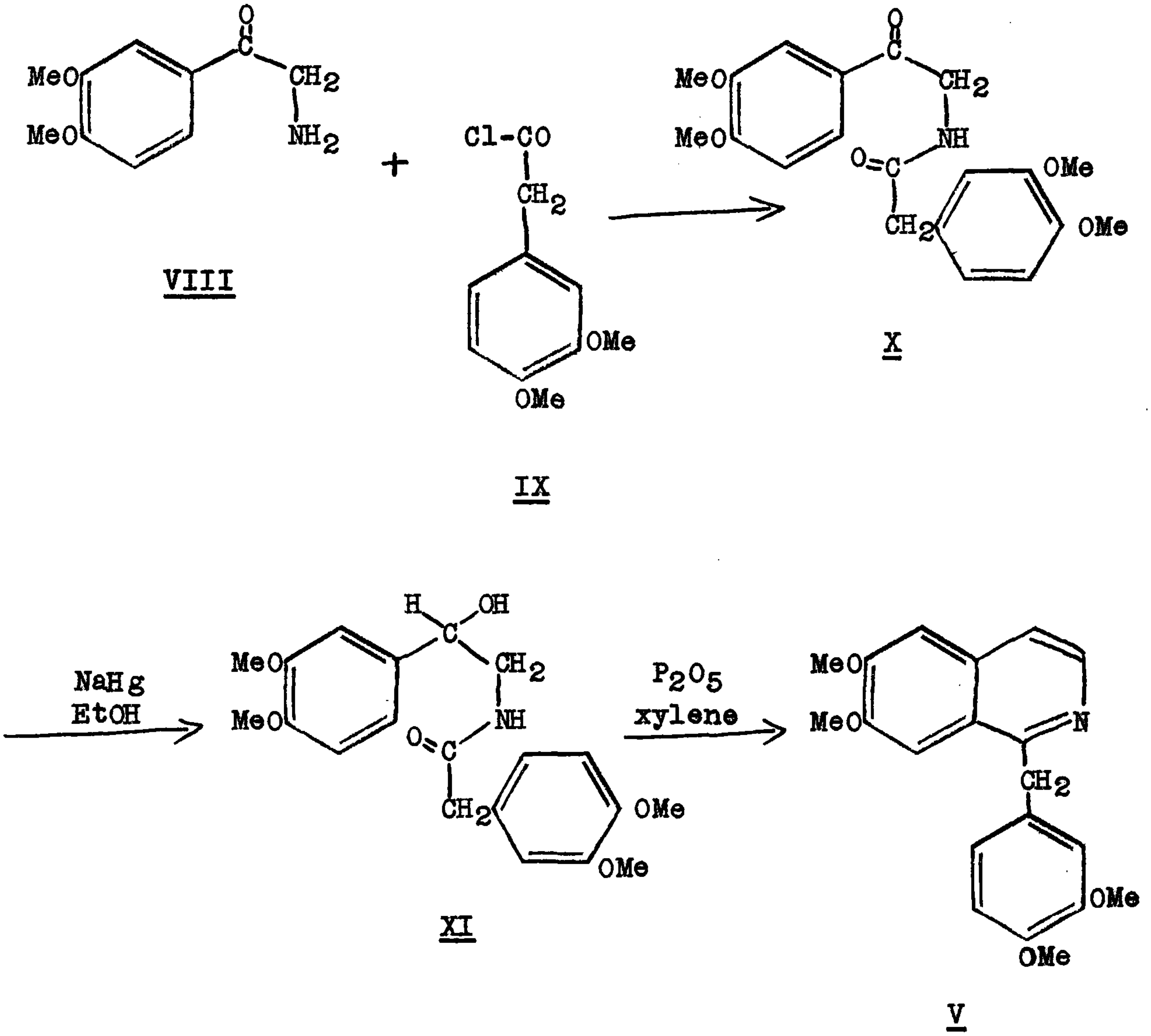
or a Schiff base:

$$R\text{-}CH_2\text{-}CH_2\text{-}N{=}CH\text{-}CH_2\text{-}R''$$

VII

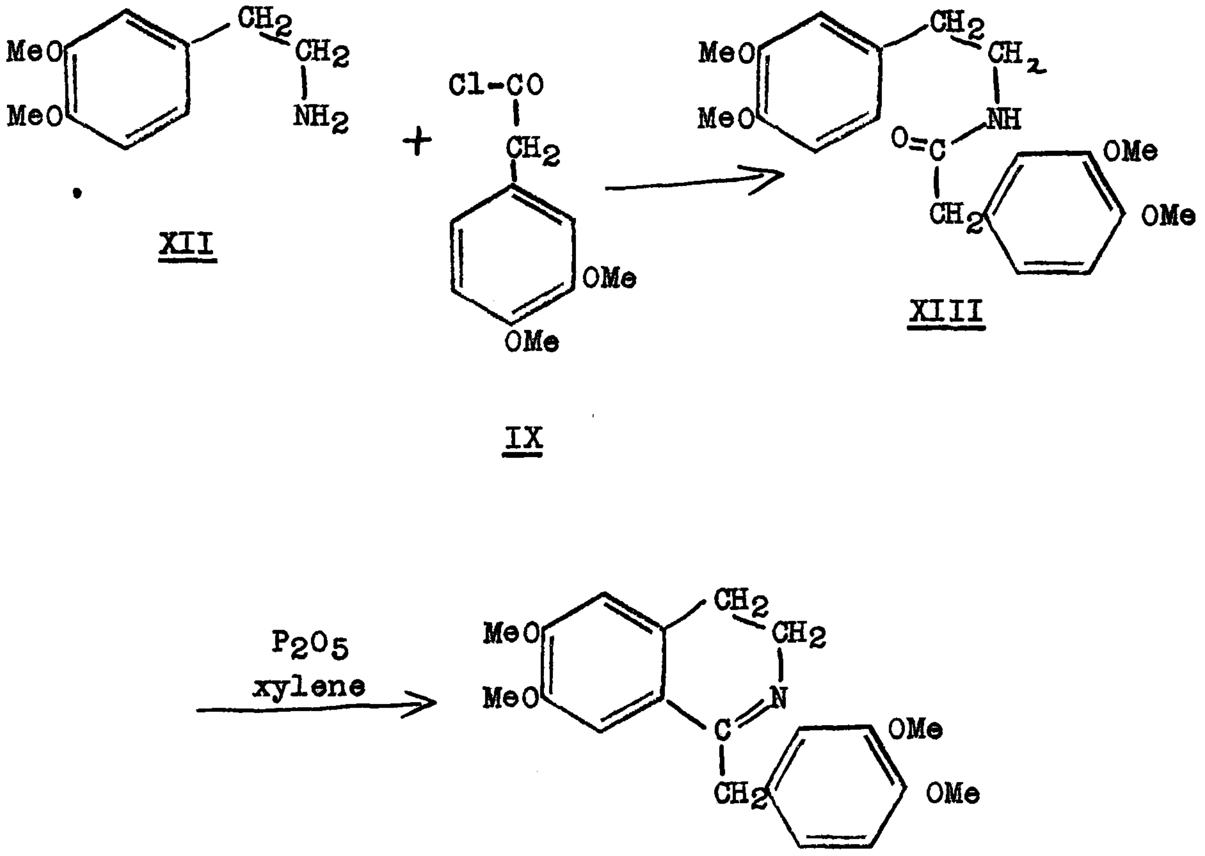
where R, R'' may be phenyl,dimethoxyphenyl, or methylenedioxyphenyl, and R' is H, OH, or OMe.

In particular, the Pictet and Gams synthesis employed veratrol and homoveratric acid as the starting materials. Veratrol (dimethyl catechol) was converted by the Friedel-Crafts reaction to acetoveratrone whose isonitroso derivative, reduced with tin and hydrochloric acid, gave aminoacetoveratrone (VIII). The hydrochloride of this amine, condensed with homoveratroyl chloride (IX) gave homoveratroyl-ω-aminoacetoveratrone (X) which could be reduced to a secondary alcohol (XI), ring closed and dehydrated with phosphorus pentoxide to give papaverine (V):



From the rather incomplete data recorded, it would seem that an over-all yield of papaverine no greater than 1% was effected by this method.

Very shortly prior to this completed synthesis of papaverine, Pictet and Finklestein (7) obtained 3,4-dihydropapaverine (XIV) by ring closure of the amide (XIII) obtained from the condensation of homoveratrylamine (XII) and homoveratroyl chloride (IX):



XII

IX

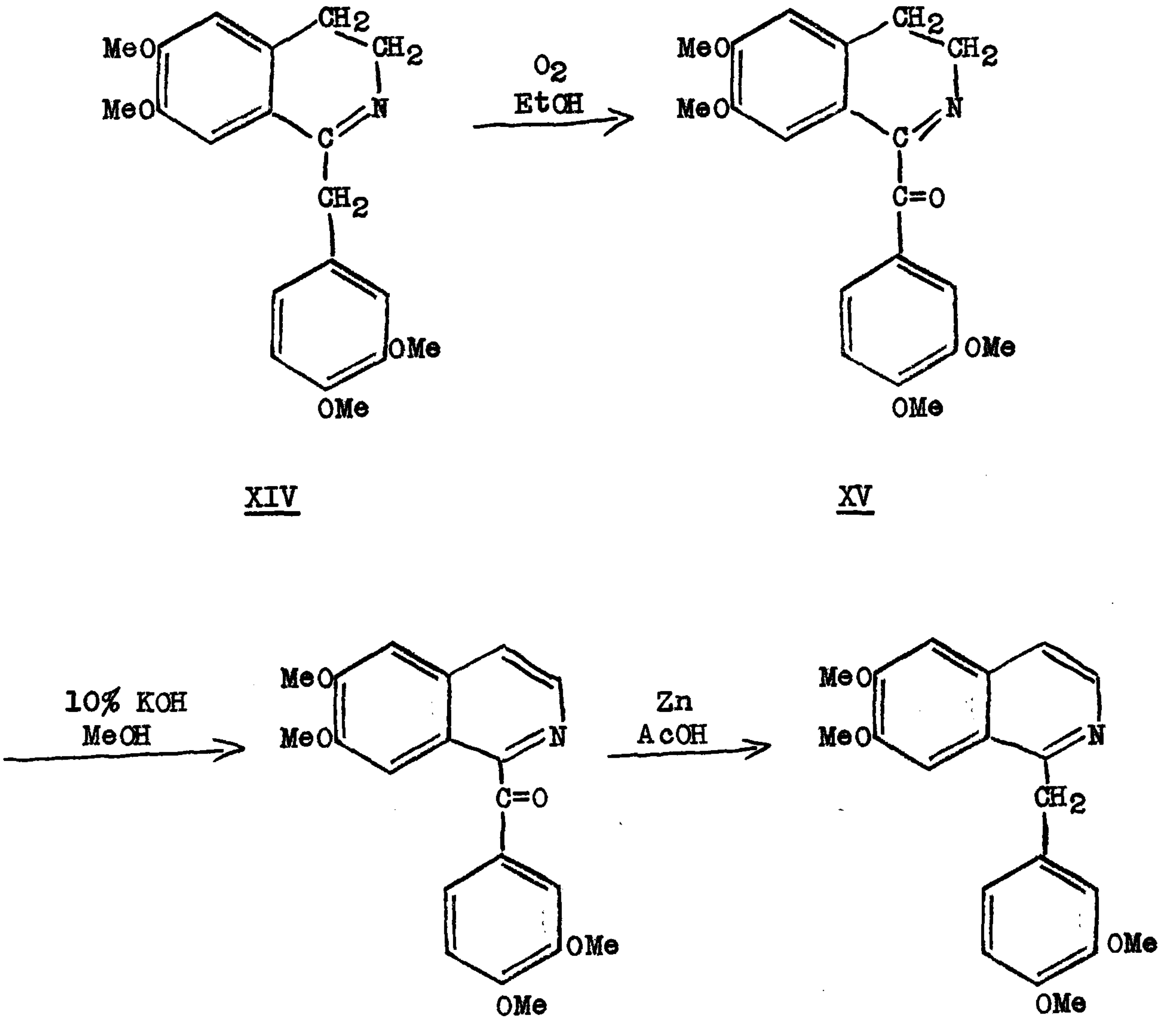
XIII

XIV

It remained for Späth and Berger (8) in 1927 to show that this compound could be dehydrogenated directly with palladized asbestos at 200°C. to give a 73% yield of papaverine. However, the over-all yield in this process would again be no greater than 1 or 2%.

Buck, Haworth, and Perkin, Jr., (9) prior to Späth and Berger's work, had found however that 3,4-dihydropapaverine (XIV) when dissolved in ethanol and exposed to the air gave

3,4-dihydropapaveraldine (XV). This could then be dehydrogenated in 10% methanolic potassium hydroxide to papaveraldine (XVI) and finally reduced to papaverine (V):



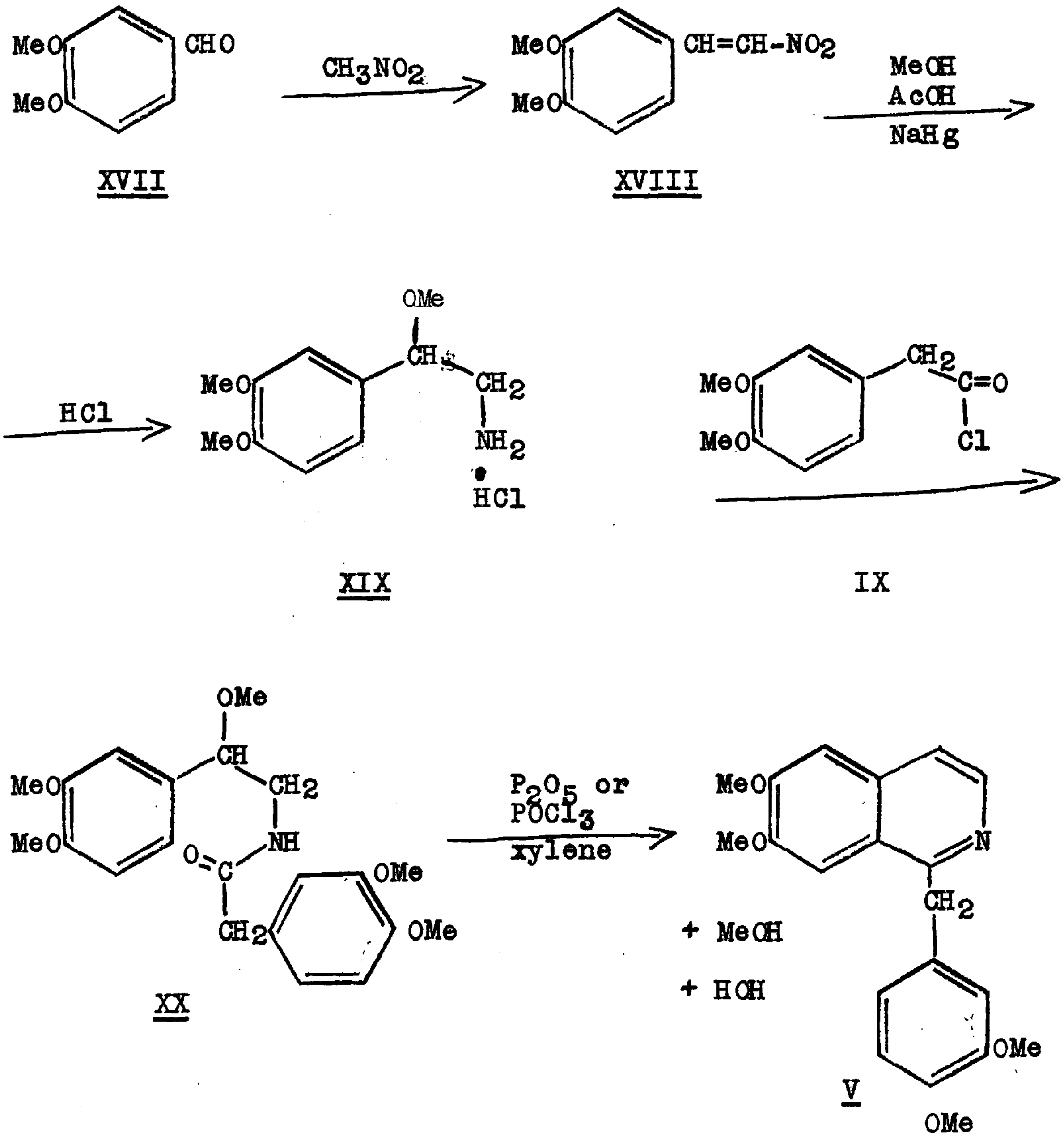
XIV

XV

XVI

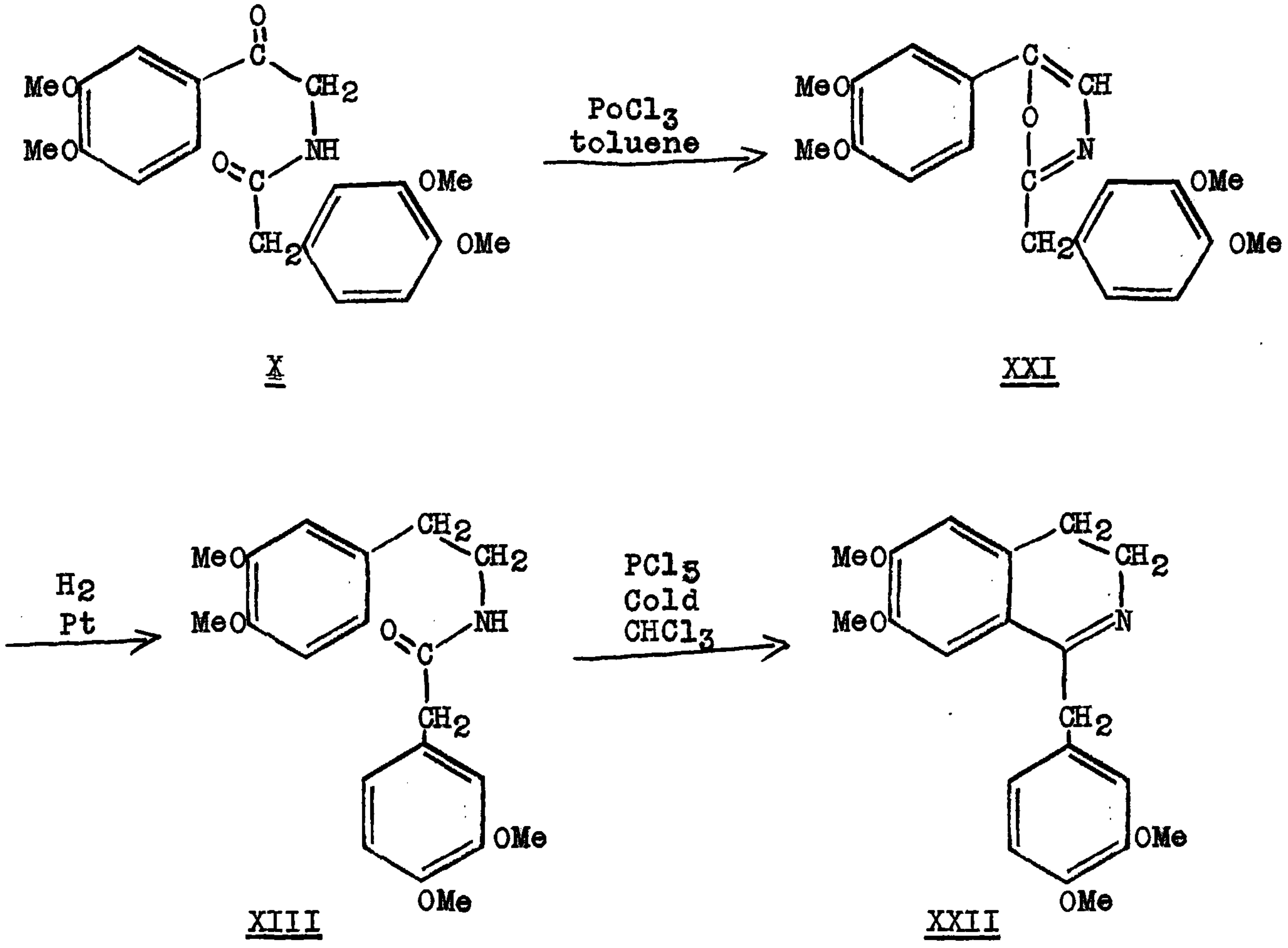
V

In 1927 two groups of investigators, Rosenmund, Notnagel and Reisenfelt (10), and Mannich and Walther (11), accomplished the synthesis of papaverine in a somewhat different manner although the basic linear skeleton prior to the ring closure was retained in this case as well. The novelty of the method arose when veratraldehyde (XVII) was condensed with nitromethane and the resulting β-nitrostyrene (XVIII) was reduced to give α-methoxyhomoveratrylamine (XIX). The hydrochloride of this base was condensed with homoveratroyl chloride (IX) and ring closed in the usual manner:



No estimate of the over-all yield could be deduced from this work but one might conjecture that it, too, might be quite low.

J.S. Buck (12) in 1930 attempted a variation of Pictet and Gams' original synthesis by what he hoped would be a direct ring closure of homoveratroyl-ω-amino-acetoveratrone (X) with phosphorus oxychloride, then to be followed by reduction, dehydration and dehydrogenation. While he obtained papaverine by this process, it remained for Young and Robinson (13) a few years later to clarify the mechanism of the reaction and show that ring closure first occurred as shown in (XXI); hydrogenation then opened the ring to (XIII) and only in the next stage was the desired ring closure to (XXII) brought about:



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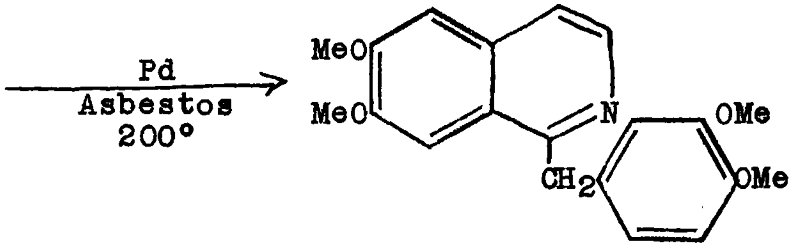
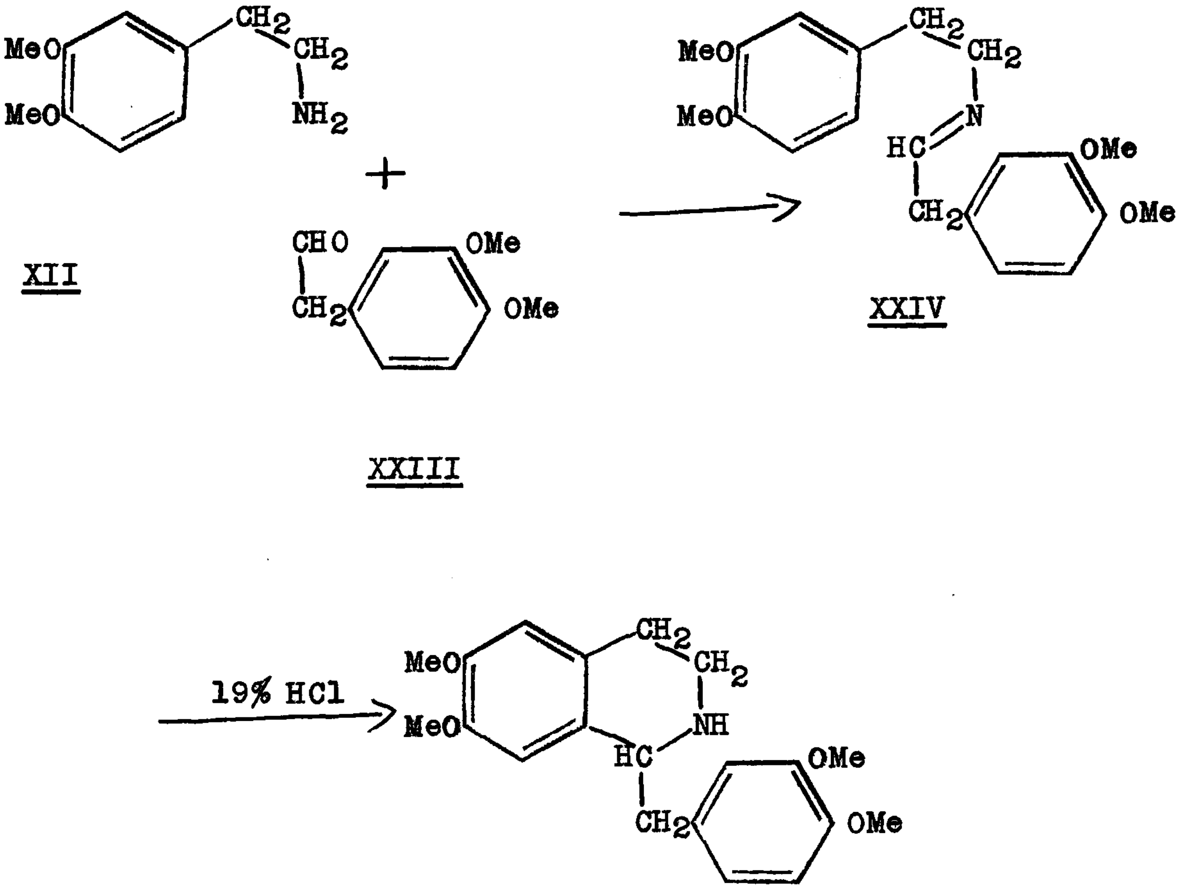


V

It is of value to observe here the remarkably mild conditions (phosphorus pentachloride in cold chloroform) that were employed to induce the ring closure, since prior to this time, boiling xylene or toluene solvents were believed to be necessary.

A very interesting synthesis of papaverine, although in quite low yield, was carried out by Späth and Berger in 1930 (14). The direct condensation of homoveratrylamine (XII) and homoveratraldehyde (XXIII) gave the corresponding Schiff base (XXIV) which was cyclized in hot 19% hydrochloric acid to give tetrahydropapaverine (XXV). The low yield of (XXV) was attributed to the instability of both the Schiff base and the aldehyde. Hahn and Schales (15) however, several years later, observed that β-phenylethylamines condensed most readily with phenylacetaldehydes at pH 5 and room temperature. Conditions such as these are exceedingly mild, and may be expected to exist in the plant cells themselves. While it is not certain that papaverine arises in the plant by the dehydrogenation of tetrahydropapaverine derived in this way, it is nevertheless a feasible route. Certainly, it indicates that optimum condensation conditions, in many cases, are far



XII XXIII XXIV XXV

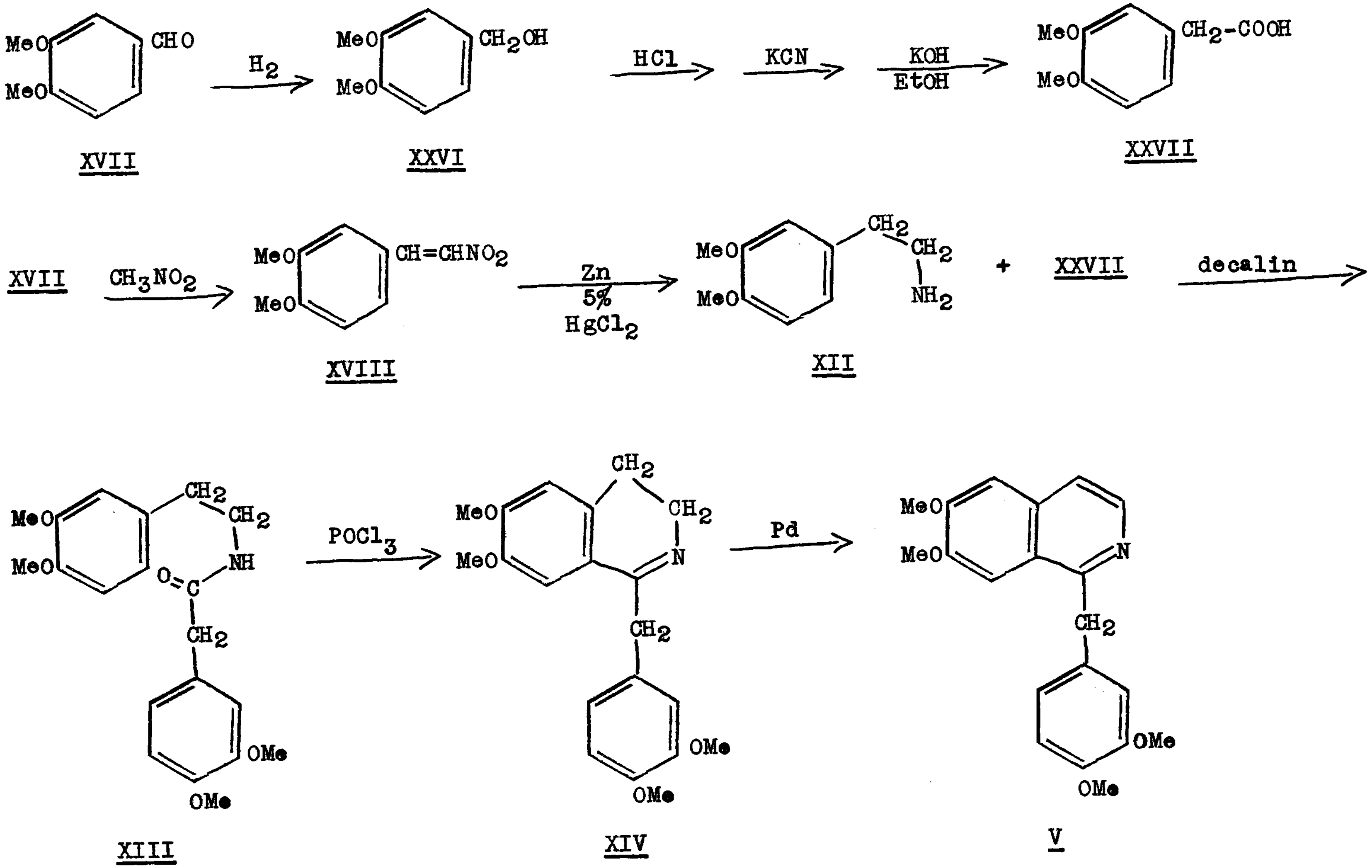
milder than they are usually imagined to be.

During the last war several processes for the commercial production of papaverine were evolved in German industrial plants and were described in recent B.I.O.S. reports (16). These processes were no doubt based, in part, on the investigations of Kindler and co-workers (17) who condensed homoveratrylamine and homoveratric acid in boiling tetralin or dihydrophellandrene. The resulting amide could then be cyclized and dehydrogenated to give papaverine. An excellent example of the advantage that may be taken of the experience of the past fifty years in these processes is the procedure used at the Merck (Darmstadt) plant.

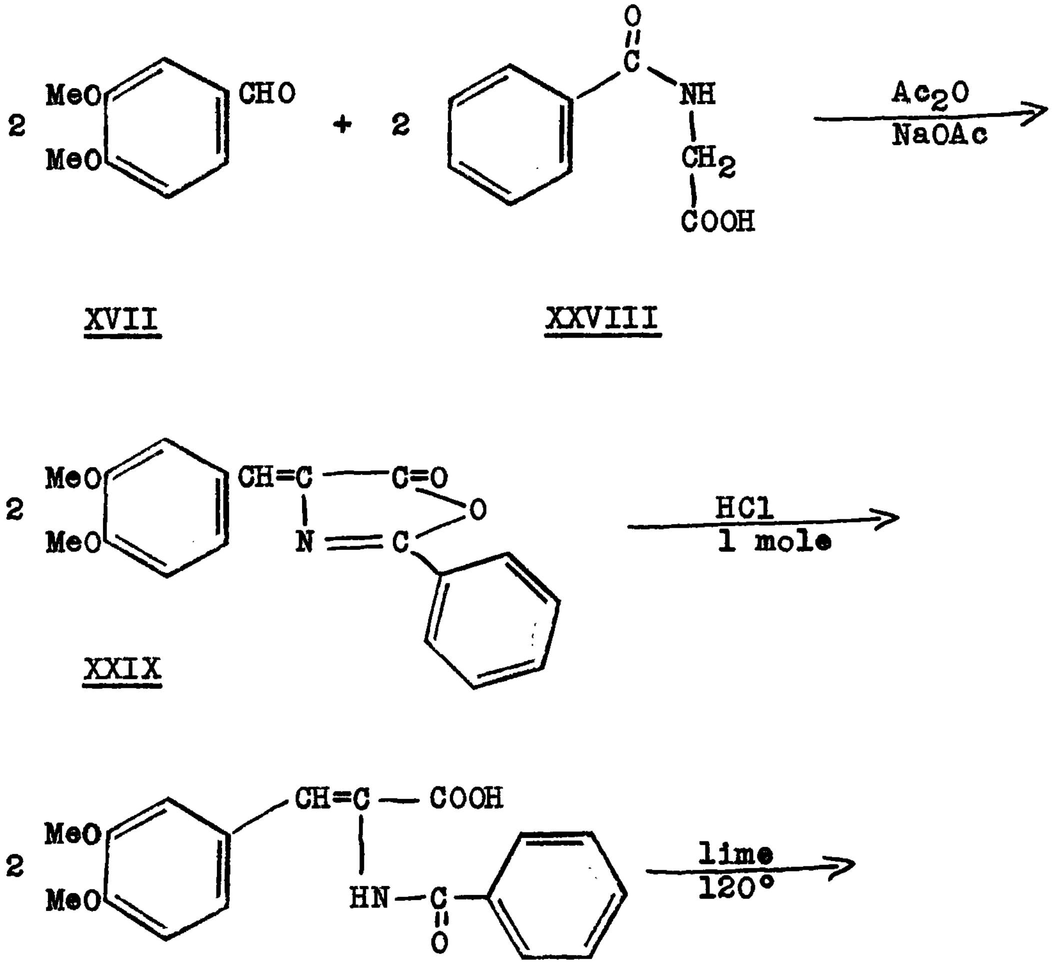
Here veratraldehyde (XVII) was reduced over a nickel-keiselguhr catalyst at 110°C. and 2200 p.s.i. to veratryl alcohol (XXVI) which, when treated with hydrogen chloride, then potassium cyanide, followed by hydrolysis with alcoholic potassium hydroxide, gave homoveratric acid (XXVII). On the other hand, when the condensation product of nitromethane and veratraldehyde was reduced with zinc dust in a 5% mercuric chloride solution, a good yield of homoveratrylamine (XII) was obtained. The condensation of this amine (XII) and homoveratric acid (XXVII) at 180°C. in a decalin solvent and ring closure of the amide with phosphorus oxychloride in refluxing trichloroethylene gave 3,4-dihydropapaverine (XIV). This substance could be dehydrogenated with palladium on pumice to give an over-all papaverine yield of 16% from veratraldehyde.

The process in the A.G. Knoll plant at Ludwigshaven was similar to the Merck process except that homoveratrylamine was prepared by hydrogenation of the veratryl cyanide intermediate in the preparation of homoveratric acid. The Hoffman - La Roche (Grenzach) process was similar in principle to the syntheses of Rosenmund et al. and Mannich and Walther (cf. p. 8). No yields or reaction details are available for the Knoll and Hoffman - La Roche syntheses but they probably could compete with the Merck method where an over-all yield of 16% was obtainable.

The final German synthesis outlined in the B.I.O.S. reports is that which was employed in the C.H. Boehringer plant at Nieder-Ingelheim. Here veratraldehyde (XVII) was condensed


MeO
MeO
CHO
H2
CH2OH
HCl
KCN
KOH
EtOH
CH2-COOH
XVII
XXVI
XXVII
CH3NO2
CH=CHNO2
Zn
5%
HgCl2
CH2
NH2
+
decalin
XVIII
XII
O=C
NH
OMe
POCl3
N
Pd
XIII
XIV
V

with hippuric acid (XXVIII) in the presence of sodium acetate and acetic anhydride to give the corresponding azlactone (XXIX) in 100% yield. After hydrolysis of the azlactone with one mole of hydrochloric acid, the product (XXX) was condensed at 120°C. with lime to give N-(homoveratroyl-)α-amino-β-veratrylpropionic acid (XXXI) in 60% yield. Ring closure of the ethyl ester of this acid with phosphorus oxychloride, followed by alkaline hydrolysis, decarboxylation and dehydrogenation with palladium black in tetralin gave the desired papaverine (V). No yields in the final steps were mentioned.



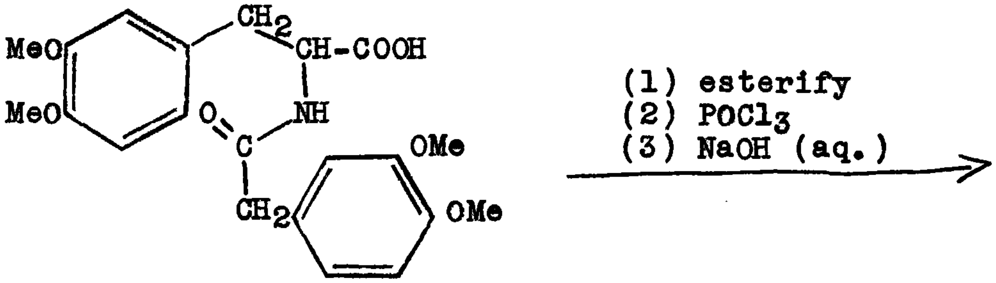
XVII

XXVIII

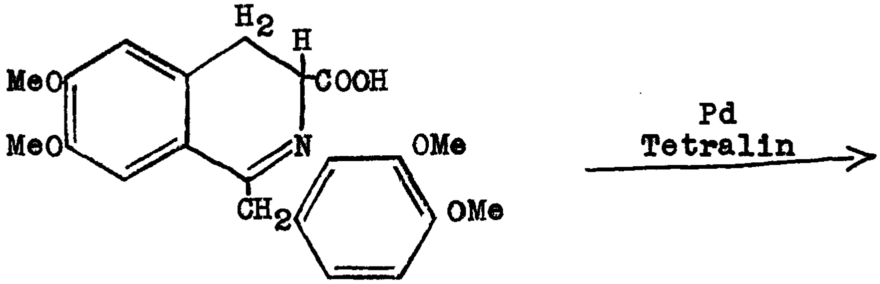
XXIX

XXX

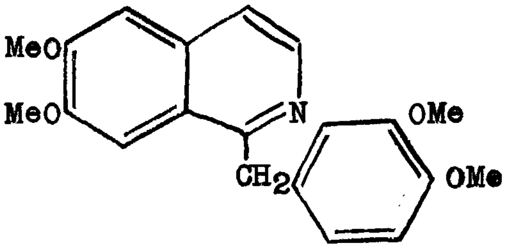
• • • •



XXXI



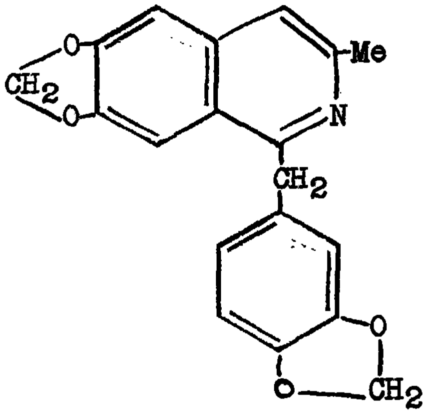
XXXII



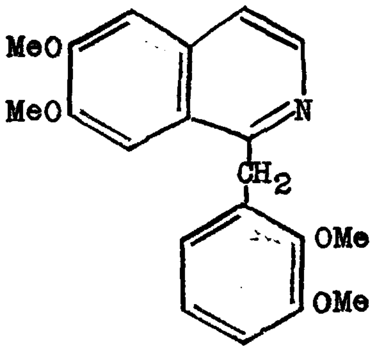
V

Syntheses of Papaverine Analogues

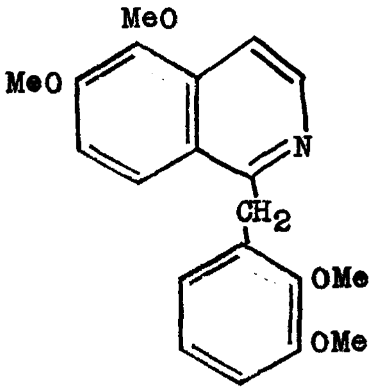
Many analogues of papaverine have been prepared during the fifty-year period in which synthetic studies in this field have been conducted. It is interesting to note, however, that these related compounds were obtained in every case by ring closure of the same types of basic structures successfully used in the syntheses of papaverine itself. (cf. p. 5). Thus Slotta and Haberland (18) and Sugasawa (19) prepared various 1-aryl isoquinolines by condensation of β-arylethylamines and alkoxybenzoic acids, followed by ring closure and dehydrogenation in the usual way. Sugasawa and Sakurai (20) synthesized 1-(3',4'-methylenedioxybenzyl)-3-methyl-6,7-methylenedioxyisoquinoline (XXXIII) by condensation of the appropriate β-aryl-α-methylethylamine under the same conditions. In a like manner, the fifteen possible ethoxymethoxy isomers of papaverine substituted in the 3', 4', 6' and 7 positions were prepared by Shepard and Noth (21); Tsatsas (22) also synthesized 1-(2',3'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (XXXIV); Kubiczek and Späth (23) 1-(2',3'-dimethoxybenzyl)-5,6-dimethoxyisoquinoline (XXXV); and Noller and Azima (24) 1-(β-methylenepyridyl)-6,7-methylenedioxyisoquinoline (XXXVI) by the same general route.



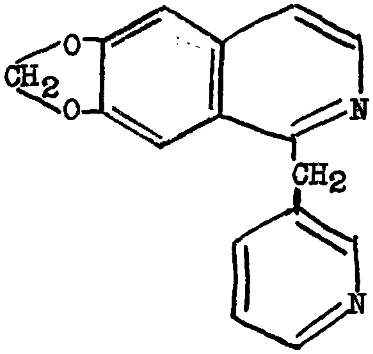
XXXIII



XXXIV

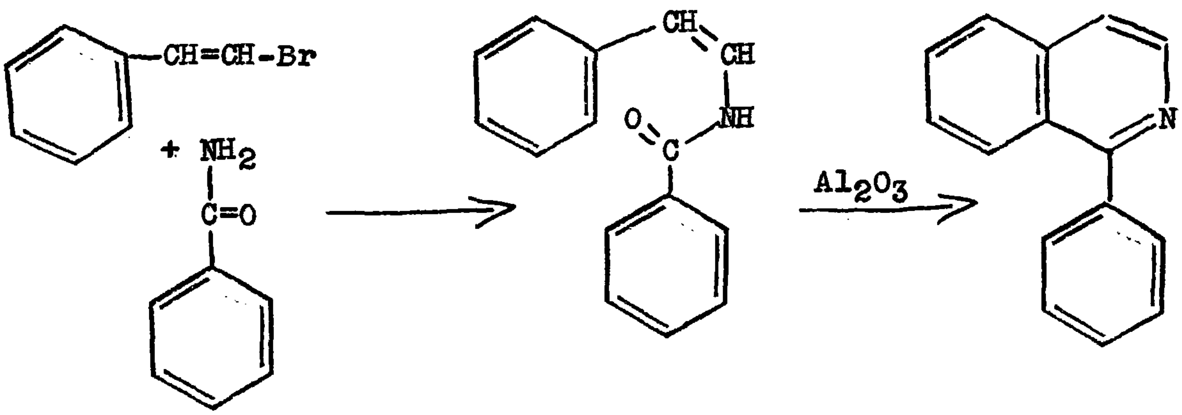


XXXV



XXXVI

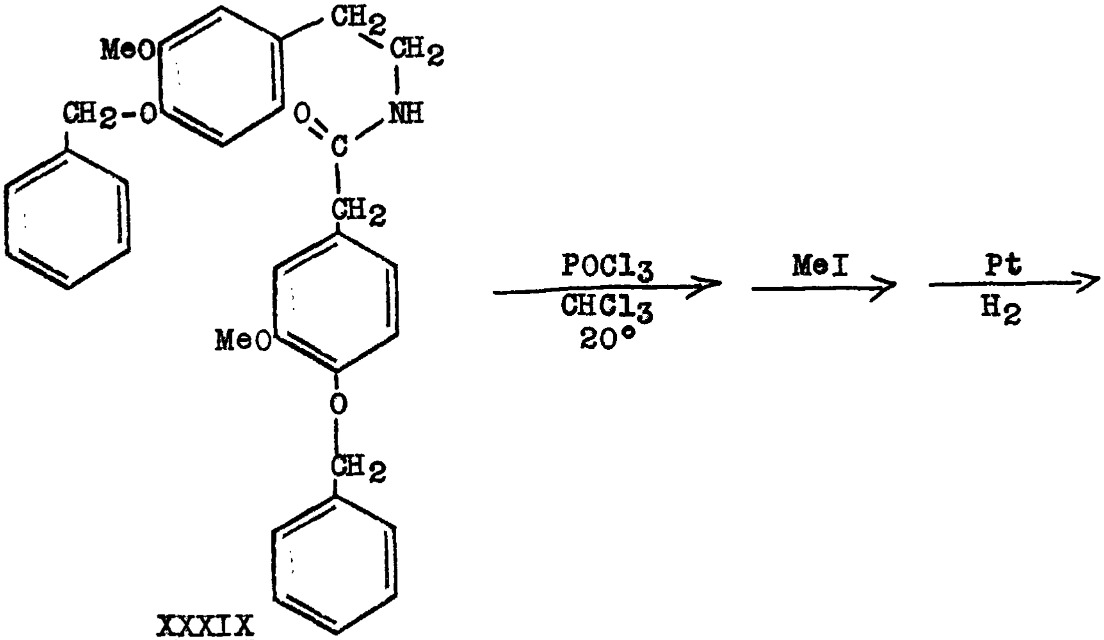
Redel and Bouteville (25) in 1949 prepared methyl papaverine-3-carboxylate and other esters in a manner quite similar to the process reported for the C.H. Boehringer plant at Nieder-Ingelheim (cf. pp. 13, 15, 16). The synthesis of (XXXIII) and the corresponding 1-phenyl derivative was accomplished by Keimatsu (26) using the method of Mannich and Walther (11), while Rosenmund (27) obtained 1-phenylisoquinoline (XXXVIII) by the ring closure of ω -benzamidostyrene (XXXVII) with specially prepared alumina:



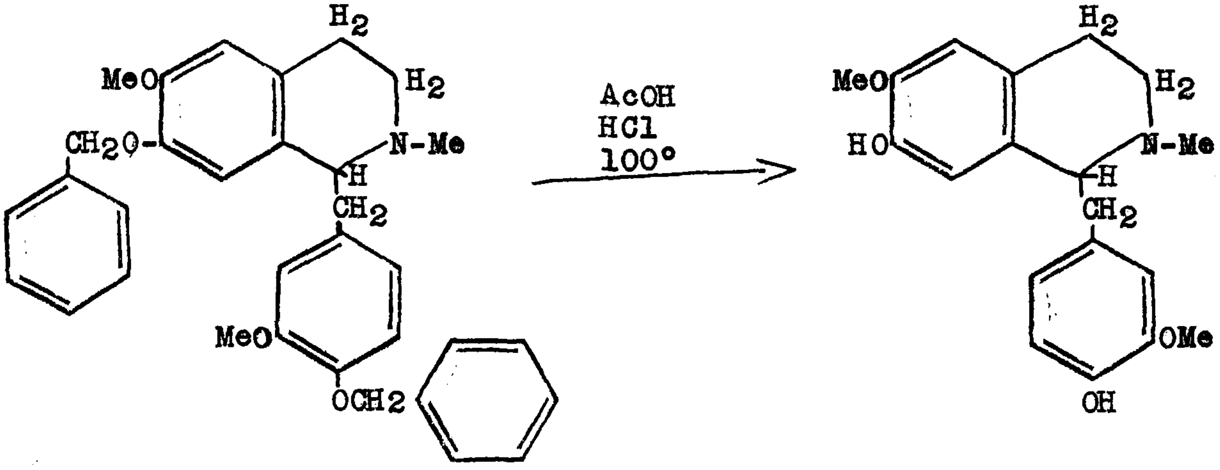
XXXVII

XXXVIII

Two interesting syntheses of papaverine analogues were performed by Robinson and Sugasawa (28) and Clemo and Turnbull (29). The usual condensations of amine and acid (or acid chloride) followed by ring closure were carried out, but in both cases the vanillin hydroxyl group was initially protected by a group which was later removed. The former prepared 1-(3'-methoxy-4'-hydroxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (XLI), using the benzyl ether of vanillin as a starting material for XXXIX. After ring closure, methylation of the amide nitrogen, and reduction, cleavage of the benzyl ether units from XL yielded the phenolic derivative (XLI).

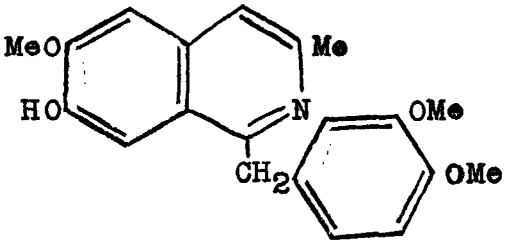


XXXIX



XL XLI

The latter workers used the benzoyl derivative of vanillin to synthesize α-methyl-β-(3-methoxy-4-benzoylhydroxyphenyl)ethylamine. The condensation product of this amine and homoveratric acid was ring closed with phosphorus oxychloride, dehydrogenated and hydrolyzed to give 1-veratryl-3-methyl-6-methoxy-7-hydroxyisoquinoline (XLII). As one might expect, the introduction of

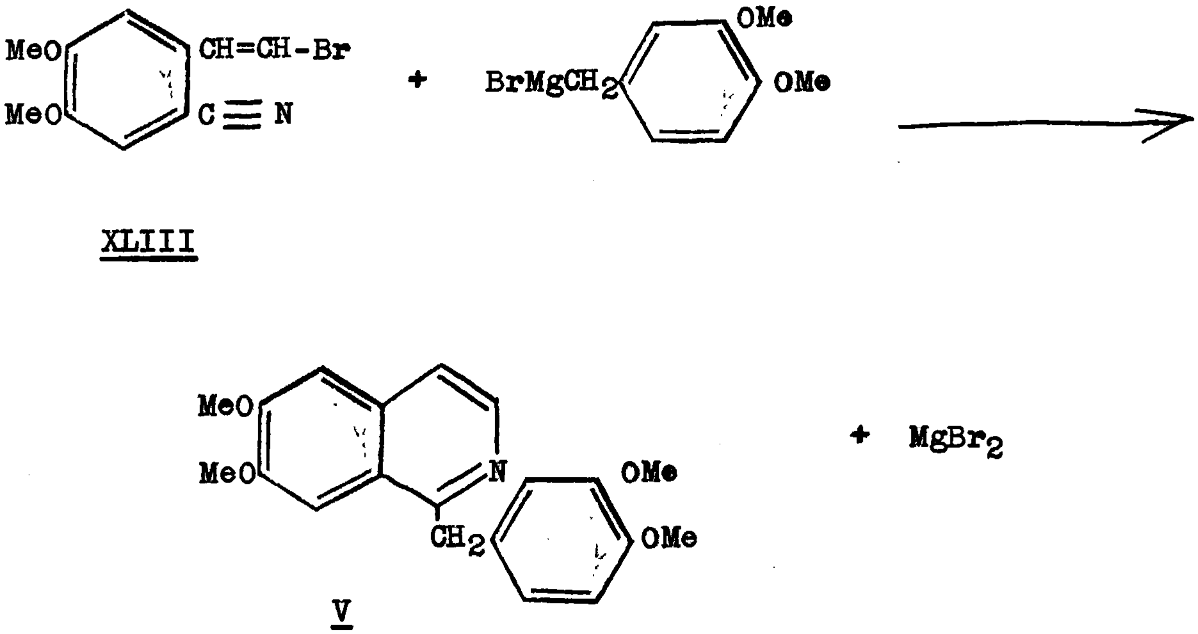


XLII

a different protecting group on the vanillin hydroxyl had no apparent effect on the directive influences involved in the ring closure of the intermediate amide. No evidence was found in this work, or for that matter in any of the other papaverine-type syntheses, that isoquinolines substituted in the 7,8 positions rather than the 6,7 positions could be obtained by varying substituents in this method of ring synthesis.

Related Studies on Isoquinoline Syntheses

An examination of the structure of papaverine might suggest that other approaches to the problem of synthesis would offer some promise of success. It appears evident that two phenyl nuclei, appropriately substituted with methoxyl groups, must be initially present and that ring closure somewhere else in the nitrogen cycle would provide the only hope of variation in the method of synthesis. One such attempt to complete the isoquinoline ring was quite novel, but also quite unsuccessful. Kefford (30) hoped to condense 2-cyano-3,4-dimethoxy-ω-bromostyrene (XLIII) with veratryl magnesium bromide, and thus to obtain papaverine (V).

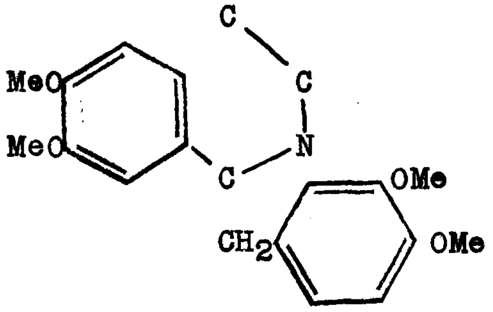


XLIII

V

However, he obtained the nitrile only in very low yield and was unable to prepare the Grignard reagent at all.

A final variation on the point at which ring closure is to be effected in the nitrogen cycle would occur in the intramolecular condensation of a compound with the skeleton (XLIV):



XLIV

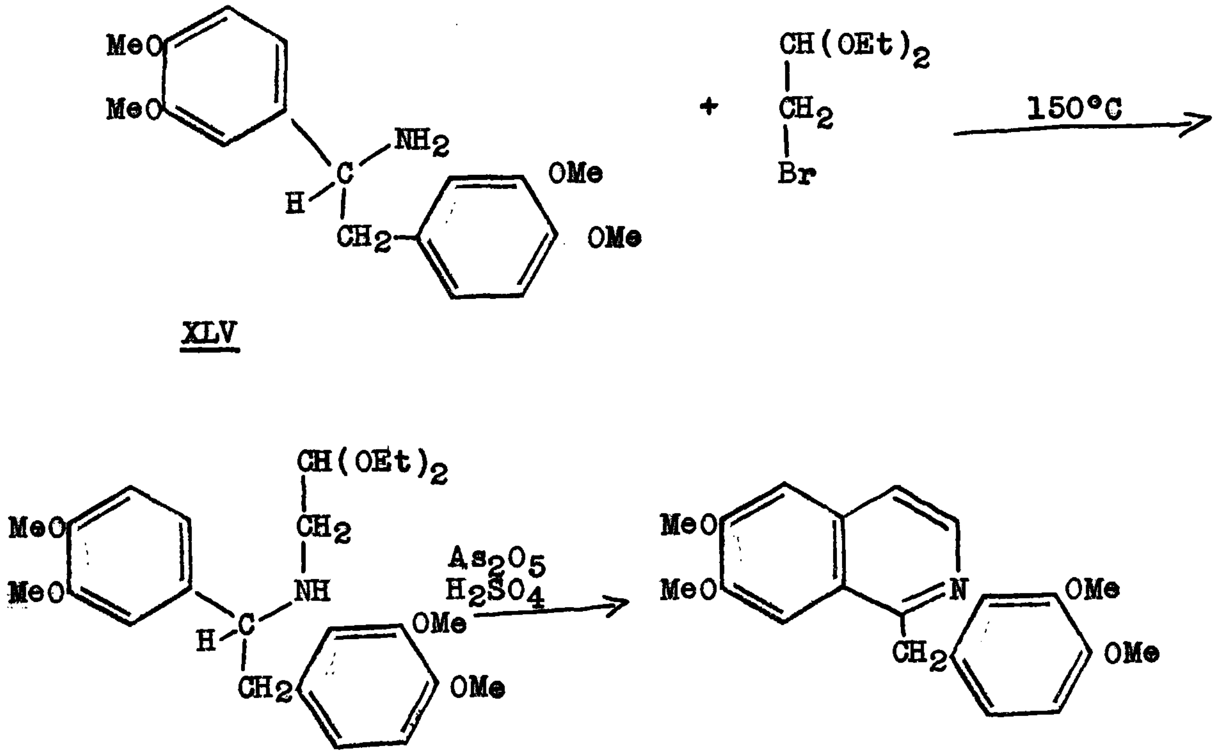
The work of Pomeranz (31) suggested the feasibility of such an attempt. He showed that ring closure, with concentrated sulfuric acid, of the Schiff base of benzaldehyde and aminoacetal gave rise to a 50% yield of isoquinoline, and he outlined the possibility of preparing papaverine from the corresponding Schiff base of desoxyveratroin. It remained for Fritsch (32), in the first reported attempt at the synthesis of papaverine, to prepare the Schiff base of desoxyveratroin and aminoacetal by condensation at 200°C. This base, an undefined oil, on subsequent ring closure in 80% sulfuric acid at room temperature gave only a very low yield of a yellow compound melting at 163°C., or 15°C. higher than papaverine, but with nearly the same elementary analysis. (Calc. for $C_{20}H_{21}O_4N$: C, 70.8;

H, 6.2; N, 4.1%; Found: C, 70.7; H, 6.4; N, 4.8%.) On the basis of these unsatisfactory analytical results, Fritsch claimed the compound was isomeric with papaverine, but no further work was undertaken to establish the structure of this so-called isomer. Fritsch did extend, however, the scope of the Pomeranz isoquinoline synthesis to include 7-alkoxyisoquinolines and 6,7-methylenedioxyisoquinoline. He also showed that derivatives of meta alkoxybenzaldehyde gave rise to only 7-alkoxyisoquinolines and that the ortho or para isomers gave no identifiable products.

Further work by Woodward and Doering (33) and Manske and Kulka (34) in later years have extended the applicability of this method still more. Of note in this respect is the relative ease with which aminoacetal condenses with substituted benzaldehydes to give the Schiff base, and the rather good yields of the corresponding isoquinolines obtained on ring closure of the compounds cited. In particular, Woodward and Doering prepared 7-hydroxyisoquinoline from m-hydroxybenzaldehyde, while Manske and Kulka synthesized 7-hydroxy-8-chloroisoquinoline from 2-chloro-3-hydroxybenzaldehyde. Equal amounts of 5- and 7-chloroisoquinoline were produced from m-chlorobenzaldehyde, by an indifferent ring closure in the 2 as well as the 5 position in the benzene ring.

Other failures, in addition to the Fritsch attempt to synthesize papaverine, have been recorded for the Pomeranz method. Perkin and Robinson (35) got only a trace of the isoquinoline after ring closure of the Schiff base obtained in good yield by condensation of 2,3-dimethoxybenzaldehyde with aminoacetal. Staub (36) in an extensive survey of various possibilities concluded that ring closure could only occur if the side chain contained conjugated (or potentially conjugated) double bonds and also an hydroxyl or alkoxyl group β to the nitrogen atom. No attempt was made to correlate the effect of substituents in the benzene ring. This task would appear to be impossible since obvious anomalies may be found. As an example, one only need quote the failure of Fritsch to obtain an isoquinoline from the Schiff base of desoxyveratroin and aminoacetal, while he obtained an excellent yield of the isoquinoline from the Schiff base of 3,-4-methylene-dioxybenzaldehyde and aminoacetal. It is difficult to imagine how the presence of a veratryl group on the side chain of the Schiff base could have such a profound effect on the reaction. Apart from the failure with the desoxyveratroin Schiff base, a successful ring closure would appear to follow only with the Schiff base of an unsubstituted benzaldehyde, of a meta hydroxy-, alkoxy- or chlorobenzaldehyde, of a 3,4-dialkoxy- , or 2-chloro-3-hydroxy- or alkoxybenzaldehyde.

A related, but more limited, isoquinoline synthesis was devised by Rügheimer and Schön (37), in which the hydrogenated Schiff bases of certain aryl aldehydes were cyclized with arsenic pentoxide in strong sulfuric acid. As an example, one may cite the preparation of 6,7-dimethoxyisoquinoline in 50% yield from N-veratrylaminoacetal. On the basis of this observation, Allen and Buck (38) undertook the preparation of papaverine. They heated bromoacetal and 3,4,3',4'-tetramethoxydesylamine (XLV) to 150°C., treated the brown oil which they assumed to be XLVI with arsenic pentoxide in concentrated sulfuric acid, and hoped that the reaction would follow the course outlined through XLVI to give V.



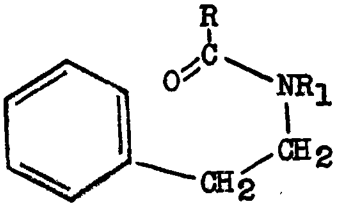
XLV

XLVI

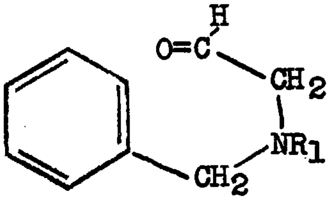
V

Unfortunately they obtained no identified products. No other condensing agents were employed and no attempt was made to characterize the intermediate oil in the series. On the basis of this scanty evidence they concluded that the method offered no further promise of a papaverine synthesis. There is, however, grave doubt that the intermediate amine would actually be obtained under the conditions they employed in the condensation and therefore the conclusion is unjustified that ring closure of this compound would be unsuccessful.

It is nevertheless true that other investigators have failed in the application of the Rügheimer method to the synthesis of certain isoquinoline derivatives. Of note is the work of Young and Robinson (13) who conclude that compounds of type XLVII condense very easily, while compounds of type XLVIII are very difficult, if not in most cases impossible, to condense.

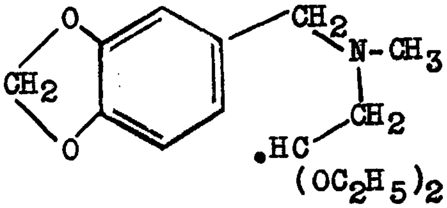


XLVII

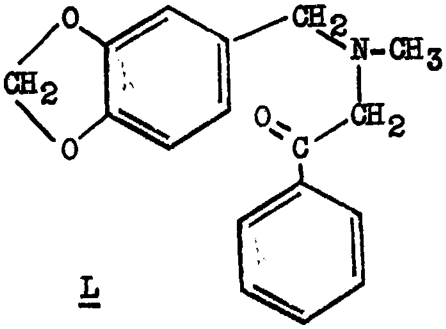


XLVIII

As an example of the difficulty of condensing type XLVIII compounds, they quote the very low yields obtained on ring closure of piperonyl-methylaminodiethylacetal (XLIX) or piperonylmethylamino- ω -acetophenone (L):



XLIX



L

using such condensing systems as 80% sulfuric acid saturated with hydrogen chloride, phosphorus pentoxide or oxychloride in toluene or benzene, concentrated hydrochloric acid alone or with acetic acid, 10% hydrochloric acid, anhydrous oxalic acid, and acetic anhydride - sulfuric acid. The fact that these saturated side chain compounds were found to be difficultly condensed agreed well with the observations of Staub on the unsubstituted phenyl derivatives (p. 24) and strengthens the conclusion that the Rügheimer method encompasses only a very narrow range of applicability.

DISCUSSION OF RESULTS

Previous synthetic work on papaverine left little to be desired as far as the preparation and condensation of acylaminoethane derivatives are concerned. Attempts, however, to prepare papaverine by closure of the isoquinoline ring in an alternative position have been singularly unproductive. In particular, one might recall the unsuccessful and quite incomplete work of Fritsch (32) and Allen and Buck (38) outlined previously. Many questions in this work were left unanswered and it was felt that a re-examination of this alternative route to papaverine would not be amiss.

Preliminary Preparations

Many methods are recorded for the preparation of desoxybenzoins. Among these are the reduction of benzils (38, 39), the reduction of benzoins (40, 41, 42, 43, 44) the reaction of benzamides with benzyl magnesium chlorides (45), the condensation of phenylacetyl chlorides with aromatic hydrocarbons under the influence of aluminum trichloride (46), and finally, the reaction of tolans with ethyl mercaptan followed by hydrolysis of the dithioketal with 25% hydrochloric acid (32). The method of Kubiczek (44) was chosen to prepare desoxyveratroin, 3,3'-dimethoxy-4,4'-dibenzyloxydesoxybenzoin, and desoxybenzoin, since good supplies of methyl vanillin, benzyl vanillin, and benzoin itself, were readily available. In the former cases, a simple benzoin condensation of veratraldehyde or o-benzyl vanillin in the presence of potassium cyanide, followed by reduction with zinc and acetic acid, was sufficient while in the latter case reduction only was necessary.

The crude veratroin from the initial condensation was purified by precipitation from ether into petroleum ether prior to reduction. The observation of Fritsch (32) that desoxyveratroin and veratril could not be separated from one another by crystallization was confirmed. Girard's reagent (47), however, was found to be an excellent means of obtaining pure desoxyveratroin, uncontaminated with other reduction products and veratril. Here desoxyveratroin alone reacted with the difunctional "T" reagent to give a water soluble carbonyl derivative stable at pH 7.0. After removal of the water insoluble fraction with benzene, acidification of the aqueous solution to pH 1.0 decomposed the derivative and precipitated pure desoxyveratroin.

The low yield of 8% of theory was at first attributed to excessive loss of veratroin during the petroleum ether precipitation, where Kubiczek found that only a 25% yield of veratroin could be obtained. A 50% yield was reported when the purification was carried out by alumina chromatography and in both cases the veratroin could be reduced quantitatively to desoxyveratroin. When however the ether extract of the present reaction mixture was evaporated under nitrogen and the residual oil was reduced with a large excess of zinc dust, the highest over-all yield of pure desoxyveratroin was only 18%, and that of the benzyl analogue 28%. Other investigators (48) also found that such zinc dust reductions were often capricious and depended markedly on the grade of dust employed. The attribution of the low yields to this factor, and not to the veratraldehyde condensation was supported by the low (41%) yield of pure desoxybenzoin obtained when crystalline benzoin was reduced under the same conditions.

As Allen and Buck (38) showed, a yield of approximately 70% of desoxyveratroin oxime was obtained by using hydroxylamine hydrochloride in pyridine at 100°C. Present experiments showed however that the yield could be increased to 100% at room temperature by prolonged stirring of a slurry of desoxyveratroin in 80% ethanol containing a five molar excess of hydroxylamine hydrochloride buffered with sodium acetate to pH 5.0. Pure desoxyveratroin oxime was readily recovered by partial evaporation of the solution after 2 or 3 days' time. The increased yield was no doubt due to the elimination of decomposition and oxidation in hot pyridine solutions. While desoxyveratroin readily formed the oxime in aqueous ethanol, the corresponding benzyl derivative was completely inert. This mischance might be attributed, in part at least, to the complete insolubility of the benzyl derivative in ethanol. The oxime of this compound was readily prepared in 85% yield with pyridine and hydroxylamine hydrochloride at 100°C.

The reduction of desoxyveratroin oxime over Raney nickel in an ethanol - acetic acid solvent at 1300 p.s.i. and

80-100°C. gave 70% of 3,4,3',4'-tetramethoxydesylamine (XLV). This method appeared more convenient than the reduction with sodium amalgam and acetic acid in ethanol employed by Allen and Buck (38) who reported a crude yield of 75% of theory. One or more recrystallizations from water were necessary to bring their product to a comparable state of purity.

Most of the chloroacetal was obtained from the Eastman Kodak Co., but the earlier supply was derived from a 40-45% aqueous solution of chloroacetaldehyde obtained from the Dow Chemical Co. The chloroacetaldehyde was salted out of this solution by saturation with ammonium nitrate and sulfate, and the ether extract, after thorough drying over calcium sulfate, was evaporated. According to Natterer (49) chloroacetaldehyde could be converted to chloroacetal in the presence of a calcium chloride catalyst and a very large excess of ethanol. He remarked that the reaction was quite slow but failed to include pertinent experimental details or his yield. With this information as a guide, the present procedure, involving the continuous removal of water formed during condensation, by slow azeotropic distillation with benzene, gave a 30% yield of chloroacetal and was considered satisfactory.

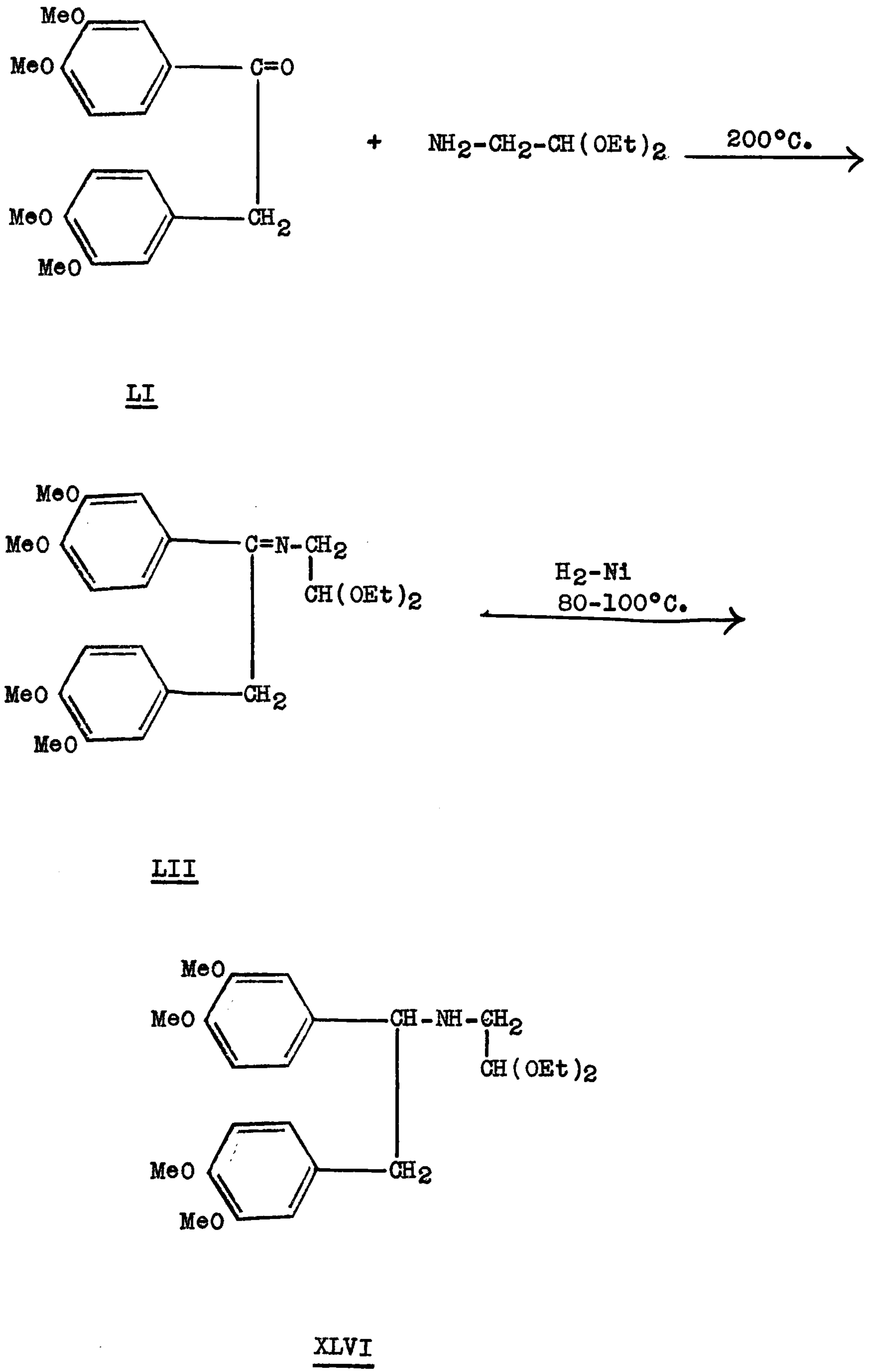
The conversion of chloroacetal to aminoacetal may be brought about with liquid ammonia at 130°C. (50); aqueous ammonia at 130°C. (51); ethanolic or methanolic ammonia at 115 to 140°C. (33, 52, 53); and aqueous ethanolic ammonia, ammonium carbonate at 115°C. catalyzed with potassium iodide (54). The latter procedure of Richmond and Wright (54), although giving somewhat lower yields than the high temperature alcohol-ammonia systems (viz. 33, 53), was employed throughout since it was the most easily adapted to the equipment at hand. Yields comparable with the 30-35% reported by Richmond and Wright were obtained in the conversion of chloroacetal, but the substitution of bromoacetal in equivalent amounts lowered the yield to 11-14% of theory. The use of a 12-hour reaction time at 140°C., or 27 hours at 120°C., did not markedly affect the yield in the bromoacetal reaction. The lowered yield was not difficult to understand, since bromoacetal in ethanolic ammonia gave only 35% of aminoacetal (53), in contrast with the 70% yield obtained from chloroacetal in methanolic ammonia (33).

Condensation of Desoxyveratroin and Aminoacetal

The attempt made by Fritsch (32) to prepare papaverine from the Schiff base of desoxyveratroin and aminoacetal was outlined in a previous section. On preliminary examination it would appear that the conditions used to prepare the Schiff base were unnecessarily severe, since many instances were cited in the Introduction to show the relative ease with which aminoacetal condensed with arylaldehydes. As already noted, desoxyveratroin oxime also formed readily. Although the oil obtained by Fritsch analyzed fairly well for the expected Schiff base (LII), (calculated for $C_{24}H_{33}O_6N$: C, 66.9; H, 7.67; N, 3.25%; Found: C, 65.5; H, 7.3; N, 3.2%), no further substantiation of its structure was undertaken beyond the observation that hydrolysis in moist air recovered some desoxyveratroin and aminoacetal. Since quantitative data and experimental detail were not quoted, the observation might have been caused by a high percentage of unreacted material in the product.

The results of various attempts to bring about this condensation (Table I) were negative except in the final case, in which the water formed was continuously distilled away from the reaction zone rather than being returned by reflux. The possible partial condensation obtained in this example was no doubt due to the continuous removal of water and the rather high temperature, since the parallel experiment at 100° (Table I, run 9) was negative.

In another trial a mixture of desoxyveratroin and a four molar excess of aminoacetal was slowly distilled, at atmospheric pressure and under nitrogen, over a one-hour period. The temperature of the pot residue rose steadily from 160°C. to 245°C. and an almost theoretical recovery of the excess aminoacetal was found in the distillate. Hydrogenation of the oily pot residue, in ethanol over Raney nickel at 1300 p.s.i. and 80 to 100°C., gave an over-all yield of 61% of N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI) crystallizing in fine, white, felted needles and melting at 69.6-70.0°C. This substance was identified by elemental analysis and, in particular, by an alkoxyl determination. If a 70% yield (similar to that obtained on the hydrogenation of desoxyveratroin oxime) is assumed, then the yield of Schiff base (LII) from the condensa-


MeO
MeO
C=O
MeO
MeO
CH2
+
NH2-CH2-CH(OEt)2
200°C.
MeO
MeO
C=N-CH2
CH(OEt)2
MeO
MeO
CH2
H2-Ni
80-100°C.
MeO
MeO
CH-NH-CH2
CH(OEt)2
MeO
MeO
CH2

LI

LII

XLVI

TABLE I

Unsuccessful Attempts to Condense Desoxyveratroin and Aminoacetal [(a)]

Run	Solvent	Catalyst	Temp. (°C.)	Time (hrs.)	Recovery of desoxy-veratroin (%)	Other products
1	Ethanol	none	20	168	100	
2	"	"	80	30	100	
3	"	trace AcOH	20	168	100	
4	"	"	80	30	100	
5	"	5 cc. AcOH	20	168	100	
6	"	"	80	30	100	
7	Pyridine	trace NaOH	115	18	79	11% veratril
8(b)	"	HCl	115	9	71	4% " 16% veratric acid
9	none	none	100	6	100	
10(c)	"	"	150-160	4	92	1% veratril 20% by weight of red gum.

(a) Moles of desoxyveratroin and aminoacetal both 0.0069 unless otherwise stated.

(b) Desoxyveratroin 0.0026 mole, aminoacetal 0.007 mole.

(c) Desoxyveratroin 0.079 mole, aminoacetal 0.36 mole.

tion would be 61/0.7 or of the order of 85-90% based on the desoxyveratroin employed. The recovery of unchanged desoxyveratroin from the non-basic fraction of the product was 9%, and in addition there was 6-7% of a nitrogen-free solid believed to be a mixture of desoxyveratroin reduction products. This evidence, and the nearly quantitative recovery of excess aminoacetal, suggests that an 85% yield of the desired Schiff base was obtained, but only at temperatures in the region of 200°C. All attempts to isolate and crystallize the pure Schiff base have failed.

There can be no doubt that the temperature and unknown catalytic effects had a marked influence on the yield of the Schiff base from this condensation. In later repetitions of the run discussed above, it was impossible to obtain the hydrogenated Schiff base in yields above 25%; and, indeed, when the temperature was maintained at 245°C. for a prolonged time, the Schiff base would appear to have been completely destroyed.

Reaction of Haloacetals with 3,4,3',4'-Tetramethoxydesylamine

In an attempt to prepare N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI) by the condensation of bromoacetal and 3,4,3',4'-tetramethoxydesylamine (XLV) at 145°C., Allen and Buck (38) obtained only a red oil which was not characterized. When chloroacetal was heated under reflux in xylene with the desylamine, a 35% recovery of the latter was effected and no other acid-soluble compound was found. If the expected compound had indeed been produced it would have appeared in the acid soluble fraction.

The present work showed that a condensation of bromoacetal with the desylamine in benzene, at room temperature, gave rise to a 60% recovery of the latter, together with a 19% yield of an acid insoluble, amorphous compound decomposing at 237°C. The compound was insoluble in all solvents except pyridine; did not contain halogen, and contained only a trace of nitrogen. Much lower methoxyl and carbon values than those usual in this series of compounds left the possible structure much in doubt. The best empirical formula was $C_{16}H_{22}O_{11}$, but this formula, derived from carbon and hydrogen values, could not be correlated with the methoxyl value. Thus it appeared that at 20°C. or 135°C. the condensation of haloacetals with 3,4,3',4'-tetramethoxydesylamine did not produce the hydrogenated Schiff base (XLVI) desired.

Ring Closure of the Schiff Base Derived from Desoxyveratroin and Aminoacetal

Once the identity of the condensation product of desoxyveratroin and aminoacetal had been confirmed as the Schiff base LII, the next task was to bring about a Pomeranz ring closure (cf. p. 22). When an intramolecular condensation of the Schiff base (LII) in phosphorus pentoxide - concentrated sulfuric acid, in 80% sulfuric acid, or in concentrated sulfuric acid was attempted, the only product identified in the earlier experiments was the yellow crystalline base, m.p. 163°C., already reported by Fritsch (32). All three condensing media were of nearly equal efficiency and a purified yield of 20% of theory (based on desoxyveratroin) was realized. Similar yields of 18-22% were obtained for reaction times ranging from 15 to 40 hours in 83% sulfuric acid. One of the latter condensations in 83% sulfuric acid was carried out employing a Schiff base preparation from which an aliquot had been removed and hydrogenated to give pure, crystalline N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI). Since the yield of the latter compound was only 22.5%, it was reasonable to assume, as before, that the yield of the Schiff base would be no greater than 22.5/0.7, or 32%. This estimate suggested that the intramolecular condensation of the Schiff base in 83% sulfuric acid proceeded quite smoothly to give a yield, in this one step, of $\frac{18 \text{ to } 22}{32} \times 100$ or at least 70% of theory; and that the low over-all yield must be attributed to the initial condensation of desoxyveratroin and aminoacetal.

Examination of the brown residues from this preparation revealed that papaverine, too, was formed in very low yield. This base was isolated by digestion of the brown solids with petroleum ether to extract a yellow-white solid. A fortuitous separation of papaverine from the yellow base in this mixture was effected on an alumina column, using benzene which had been previously dried over calcium chloride as an eluant. Under these conditions, papaverine was retained on the column, while the yellow base was washed through. The papaverine was adequately identified by analyses and mixed melting point determinations. A 1.1% over-all yield of papaverine, or at least a 3.5% yield from the Schiff base, was obtained in 83% sulfuric acid. Thus it would appear that about 20 moles of the yellow base were formed for every mole of papaverine.

Repeated crystallization from ethanol raised the melting point of the persistently yellow base to 165°C. Unlike substituted isoquinolines of the papaverine type, the hydrochloride of this base (melting point 212°C.) was only sparingly soluble in water, was somewhat unstable, and furthermore was deep orange in color. Molecular weight determinations and analyses of the free base and its hydrochloride left no doubt that the compound was an isomer of papaverine, $C_{16}H_9N(OCH_3)_4$.

Infra red absorption studies in Nujol mulls, very kindly carried out by Mr. A.W. Pross at the laboratories of Canadian Industries Ltd., McMasterville, Que., on papaverine, the yellow isomer $C_{20}H_{21}O_4N$, and the compound $C_{20}H_{23}O_4N$ to be discussed later, disclosed the following points:

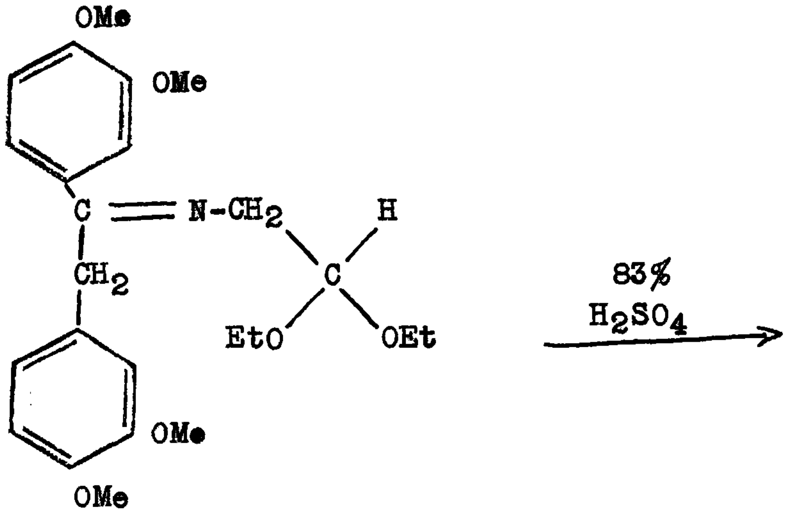
> " Benzene may be triply substituted in the following ways: symmetrical, vicinal, unsymmetrical. These ring systems give rise to specific bands which are sufficiently spaced to make differentiation possible. The evidence is definitely in favour of the presence of an unsymmetrical trisubstituted benzene ring in the yellow base $C_{20}H_{21}O_4N$, further confirmation being provided by the presence of two very close bands at 805-810 cm^{-1}, which would be expected

from two such systems in the same molecule. The spectrum of papaverine, on the other hand, shows the presence of only one such band in this region.

The N-H band is absent from the spectrum, whereas the spectrum of pyrrole shows it strongly. There are strong similarities between the spectrum of this base, $C_{20}H_{21}O_4N$, and pyrrole, so much so that if the N-H band had been present it would be reasonably certain that the base contained a pyrrole ring. It appears therefore that a five-membered pyrrole-type ring may still be present but arranged in such a way that the N-H group is absent.

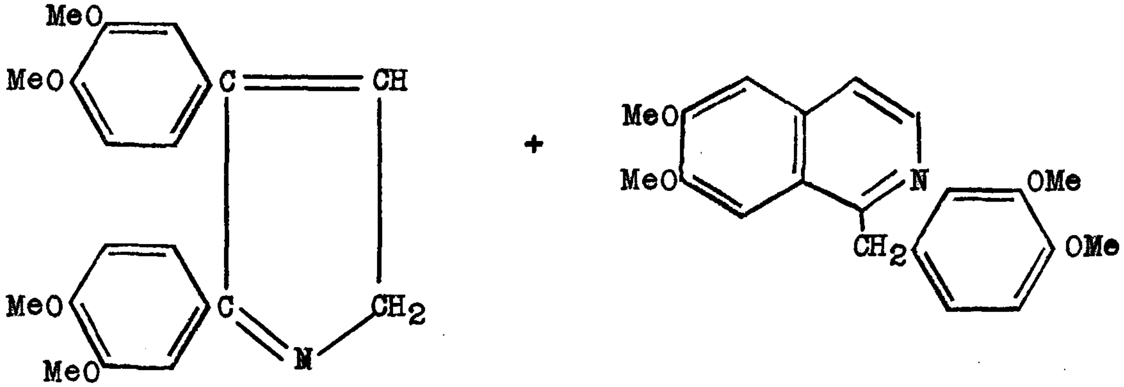
If this compound contained a five-membered ring in which nitrogen is present, but no N-H group, the spectrum should show the N=C band. Imines, e.g. pyrrole, show not only the N-H stretching frequency, but two further bands; a strong band at 1625-1690 cm^{-1} and a medium band at 1500-1590 cm^{-1}. Substituted imines show a single band in this region at 1600-1660 cm^{-1}. In the base, $C_{20}H_{21}O_4N$, the strong band at 1625-1690 is absent but there is a band sufficiently close i.e., at 1566 cm^{-1}, that can be attributed to N=C. This is additional evidence for an imine formulation of a pyrrole ring system."

Support for these observations was found in the absence of active hydrogen in a Zerewitnoff determination; the inability to prepare acetyl, benzoyl, or methyl iodide derivatives of the compound; the ease of reduction to a mixture of colorless secondary amines; the yellow color of the base; and the orange color, insolubility and instability of the base hydrochloride. All this evidence suggested that the predominant course taken by the ring closure of the Schiff base (LIII), was the hydrolysis of the acetal unit to a free aldehyde, which then condensed with the reactive methylene carbon atom of the benzyl group. The yellow base, $C_{20}H_{21}O_4N$, would then be 2,3-di(3,4-dimethoxyphenyl)-5-pyrrolenine (LIV). The isomeric papaverine (V) was produced in minor yield by the condensation of the aldehyde with the reactive carbon atom in the sixth position of the veratryl nucleus:



LIII

....



LIV — V

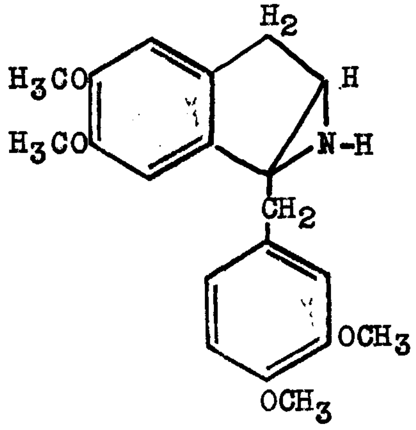
yd. = 70% — yd. = 3.5%

By condensing desoxybenzoin and aminoacetal, and by the ring closure of the resulting oil, it was hoped to prepare the simpler diphenyl analogue of the papaverine isomer just discussed. Only a brown amorphous material, which was insoluble in dilute acids, and most organic solvents, was obtained. This failure was probably not caused by lack of condensation of the desoxybenzoin and aminoacetal, since the theoretical amount of aminoacetal was consumed in the reaction. However, the resulting Schiff base might have been more easily decomposed than the corresponding methoxylated derivative, which was stable unless the temperature during the preparation was maintained at 245°C. for prolonged periods of time.

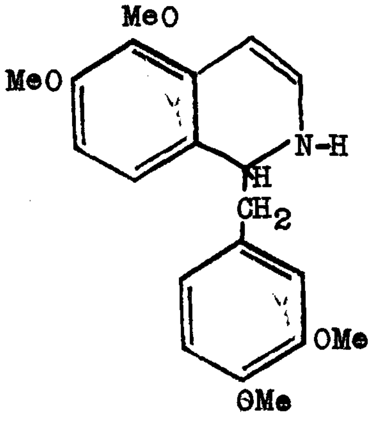
Ring Closure of the Hydrogenated Schiff Base Derived from Desoxyveratroin and Aminoacetal

When Allen and Buck attempted a Rügheimer synthesis of papaverine (cf. p. 25) they assumed that the brown oil obtained on condensation of bromoacetal and 3,4,3',4'-tetramethoxydesylamine (XLV) contained the secondary amine N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI). In an earlier section of this thesis (cf. pp. 36, 37) it was shown that in all likelihood none of this material was present at all in the products of their reaction. In the present experiments, the same compound, derived in crystalline form by hydrogenation of the Schiff base of desoxyveratroin and aminoacetal, when subjected to the conditions of a Rügheimer synthesis, yielded up to 56% of a white crystalline solid analyzing as dihydropapaverine, $C_{20}H_{23}O_4N$, but melting at 156°C.

The ease of formation of an acetyl derivative from this new substance indicated the presence of a secondary amino-group. Two compounds, also analyzing for $C_{20}H_{23}O_4N$, which need not be considered were pavine (LV) melting at 201°C. (55) and 1,2-dihydropapaverine (XXII) which melts at 97°C. (56) and has no active hydrogen. The possibility of the compound being a crystalline form of 3,4-dihydropapaverine (XIV) could not be excluded, but three groups of investigators (7, 8, 9) found this derivative to be an oil distilling at 200°C. and 0.001 mm. pressure. The two most likely structures for the compound would seem to be LVI or LVII:

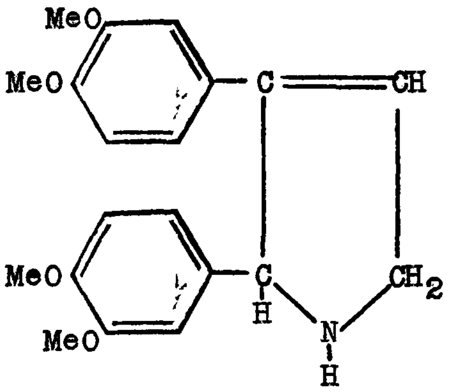


LV



LVI

or



LVII

By analogy with the work reported for the ring closure of the unhydrogenated Schiff base, the pyrroline formulation (LVII) was preferred to that of the dihydroisoquinoline (LVI). This formulation was also favored by Mr. Pross whose infra red studies were extended to this compound. His report states:

" The overall pattern of the spectrum favours a structure similar to LIV, i.e. indicative of LVII.

> The spectrum of this compound also showed a double band at 799-808 cm^{-1}, where a band due to an unsymmetrical benzene ring absorbs. By similar reasoning to that put forward for the former compound therefore, it would seem that the molecule has two substituted benzene rings.
> The N-H stretching frequency was present in the spectrum confirming the chemical evidence for a readily replaceable hydrogen atom in the molecule. The infra red evidence is therefore in favour of LVII."

Finally, the complete destruction of this compound when attempts were made at dehydrogenation under conditions suitable for dihydroisoquinolines, argued against the structure (LVI). All the available evidence, therefore, suggested that the compound $C_{20}H_{23}O_4N$, melting point 156°C., was 2,3-di(3,4-dimethoxyphenyl) -Δ^3-pyrroline (LVII).

Table II summarizes some experiments which had the object of finding the minimum conditions for acid being used without the addition of arsenic pentoxide. If the very reasonable assumptions were made that failure to recover the starting material corresponded to an initial hydrolysis of the acetal grouping, and failure to isolate LVII meant that the condensation of the free aldehyde had not occurred, it appeared that sulfuric acid from a strength of 20% up to 65% was capable of hydrolyzing the hydrogenated Schiff base, but was unable to cyclize the resulting aldehyde to an identifiable product. The acid caused only a slow hydrolysis, since 15% of the origin-

TABLE II

Treatment of the Hydrogenated Schiff Base[(a)] of Desoxyveratroin and Aminoacetal with 20-83% Sulfuric Acid[(b)]

Sulfuric Acid (cc.)	Sulfuric Acid (%)	$C_{20}H_{23}O_4N$ Yield (%)	Other Products
2.5	83	0.0	10% by weight of yellow gum
3.0	75	6.4	do
3.5	65	0.0	do
5.0	50	0.0	do
7.5	35	0.0	do
15.0	20	0.0	10% by weight of yellow gum plus 15% recovery of starting material

(a) The crystalline base, 0.00046 mole, was used in each case.
(b) For 17 hours at 20°C. in each case.

al base could be recovered after 17 hours in 20% sulfuric acid. As the acid strength increased to 75%, a low yield of $C_{20}H_{23}O_4N$ was obtained, and at 83% no identifiable product was again to be found after 17 hours. Thus, at sulfuric acid concentrations of about 75%, and higher, hydrolysis and ring closure took place but prolonged exposure of the product to the acid occasioned subsequent decomposition.

The rate at which the hydrolysis occurred in 37% hydrochloric acid at 20°C. was more closely studied by estimating the liberated ethanol with the results found in Table III. Here

TABLE III

Treatment of the Hydrogenated Schiff Base of Desoxyveratroin and Aminoacetal with Concentrated Hydrochloric Acid[a]

Time (hrs.)	Ratio of the Ethanol Found to That Calculated for Complete Hydrolysis
0.5	0.14
3.0	0.71
6.0	0.98
24	1.00
51	0.99

(a) The base, 0.02 gm., was dissolved in 1 cc. of the acid at 20°C. in each case.

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hydrolysis was complete after six hours' time. None of the pyrroline compound, $C_{20}H_{23}O_4N$, was isolated in these reactions but the colorless gum that was precipitated when the solution was made alkaline did not exhibit any evidence for a free carbonyl group. It must be imagined that condensations involving the carbonyl group, but other than the expected ring closure, took place in the concentrated acid.

Attempts to prepare the free aldehyde of the hydrogenated Schiff base by conversion first to the thioacetal, followed by neutral hydrolysis with mercuric chloride and cadmium carbonate, led to inconclusive and conflicting results (see, Experimental pp. 73-75). To afford support, then, for the above conclusions recourse was made to direct hydrolysis of the acetal in dilute (2N) hydrochloric acid at 100°C. when 92% of the ethanol theoretically possible was liberated after 7 hours. The product set free when the solution was made alkaline exhibited a very strong positive test for the carbonyl function. In this case the hot, dilute acid was capable only of hydrolysis of the acetal grouping presumably to yield the free unpolymerized and uncyclized aldehyde in 84% yield. Although attempts to crystallize the aldehyde failed, the crude oil was cyclized in 83% sulfuric acid over a 4-hour period to afford an unusually good (38%) yield of the pyrroline compound, $C_{20}H_{23}O_4N$.

Table IV summarizes various trials to determine the optimum conditions for the hydrolysis and cyclization of the original acetal. The more concentrated acid gave a maximum yield of 56% after 7 hours, while the 75% acid yielded a maximum of only 30% after 8 hours. The instability of the product in 83% sulfuric acid, however, was demonstrated by recovery of only 48% and 18% after 2 and 18 hours at 20°C., respectively. Although lack of material prevented further experiments, the results suggested that a much shorter reaction time in concentrated sulfuric acid would afford a further improvement in the maximum yield. An improvement might also be furnished by prior hydrolysis of the acetal grouping in hot dilute acid, followed by ring closure, since one such reaction (pp. 70-71) gave an over-all yield of 32% with a ring closure step of only 4 hours. Comparison with the 34% yield obtained from the acetal compound after 5 hours in 83% sulfuric acid (Table IV) suggests that the

TABLE IV

Cyclization of the Hydrogenated Schiff Base in 75% and 83% Sulfuric Acid at 20°C.

Hydrogenated Schiff Base (moles x 10^4)	Sulfuric Acid		Reaction Time (hrs.)	Yield of $C_{20}H_{23}O_4N$ (%)
	(cc.)	(%)		
9.2	6	75	4	1.6
9.2	6	75	6	6.8
9.2	6	75	8	30.
9.2	6	75	11	12.
23.1	11	83	5	34.
23.1	11	83	6	42.
23.1	11	83	7	56.
23.1	11	83	8	54.
23.1	11	83	10	18.
23.1	11	83	13	2.
4.6	2.4	83	17	0.
23.1	17	83	4.5	25.(a)
34.6	17	83	6.	48.(b)

(a) Arsenic pentoxide (0.0044 mole) was added.
(b) Arsenic pentoxide (0.0087 mole) was added.

condensation was set ahead by approximately the length of time it would take for hydrolysis of the acetal group.

Finally, the addition of arsenic pentoxide to the reaction mixture had no appreciable effect on the yield of the pyrroline, which was 25% after 4.5 hours and 48% after 6 hours. In reactions involving similar compounds (cf. pp. 24-27), where cyclization initially occurred to give an intermediate dihydroisoquinoline, the presence of arsenic pentoxide serve to dehydrogenate (or oxidize) this intermediate to the corresponding isoquinoline. The fact that no oxidation occurred in the present instance furnished further support to the view that $C_{20}H_{23}O_4N$ was best represented as the pyrroline (LVII).

EXPERIMENTAL

Preparation of Desoxyveratroin (44)

A. A solution of 60 gm., or 0.36 mole of veratraldehyde, and 13 gm., 05 0.22 mole, of potassium cyanide in 180 cc. of ethanol and 60 cc. of water was heated under reflux in a 500 cc. three-neck flask for 4.5 hours. During this time, hydrogen was bubbled into the deep red solution through a tube extending to the bottom of the flask. After the solution was cooled, it was saturated with carbon dioxide, diluted with 500 cc. of water and extracted with six 100 cc. volumes of ether. After drying over anhydrous sodium sulfate the clear yellow ether extract was mixed with 700 cc. of petroleum ether (b.p. 30-35°C.) and allowed to stand overnight at -7°C. The yellow oil which settled was separated by decantation, redissolved in 200 cc. of ether, reprecipitated with 100 cc. of petroleum ether and finally dried in vacuo to a constant weight of 32 grams. Yield of crude veratroin, 53%.

A solution of this oil in 400 cc. of methanol, 200 cc. of glacial acetic acid and 100 cc. of water was heated on a steam bath under reflux and 56 gm. of zinc dust was added over the course of 2 hours during which time the solution changed from yellow through green to colorless. After complete addition of the zinc dust, the solution was cooled, filtered, and evaporated to a volume of 50 cc. in vacuo. The concentrate was then poured into 600 cc. of stirred water and the solid which separated was recovered on a filter and air-dried. Weight, 12.5 gm. (22%) and melting point 84-92°C. One recrystallization from methanol left 10.5 gm. melting 94-99°C. Further recrystallization from methanol, ethanol, benzene or ethanol-benzene failed to raise the melting point above this to the 105°C. value quoted by Kubiczek (44).

B. In an exactly similar run, 11.3 gm., or 0.036 mole, of the crude desoxyveratroin was dissolved in 100 cc. of absolute ethanol and 10.0 cc. of glacial acetic acid (0.175 mole) and was heated under reflux with 6.7 gm., or 0.040 mole, of Girard's "T" reagent (47) for 2 hours. After cooling, the red solution was poured into 300 gm. of ice and water containing 21.5 gm. of potassium carbonate and the mixture was extracted with benzene. The clear, almost colorless aqueous solution was then acidified to pH 1.0 with hydrochloric acid and a white solid separated. After filtration and air-drying, the product weighed 4.6 gm. and melted from 103.5-104.5°C. This preparation represented a yield of pure desoxyveratroin of 8.1% of theory.

C. The yield was increased to 18% of theory by eliminating the petroleum ether precipitation. The dried ether extract from a run employing 1.2 moles of veratraldehyde was evaporated _in vacuo_ under nitrogen and the total residual oil recovered with Girard's reagent to yield 33 gm. (0.104 mole) of desoxyveratroin melting from 103 to 104°C. No higher yield than 18%

was ever obtained in this preparation.

Preparation of O-Benzyl Vanillin (28)

A solution of 45 gm., or 0.296 mole, of vanillin was heated under reflux in 90 cc. of methanol for 6 hours with 39 gm. (0.308 mole) of benzyl chloride and 21 gm. of finely divided potassium carbonate. The mixture was then cooled and filtered. White crystals appeared in the filtrate on evaporation, and were recovered on a filter and dried *in vacuo*. Weight, 50 gm. (70%) and melting point 60-61°C. The accepted melting point is 61-62°C.

Preparation of 3,3'-Dimethoxy-4,4'-dibenzyloxydesoxybenzoin

The method of Kubiczek (44) for the preparation of desoxyveratroin was employed in this case also. A solution of 35 gm., or 0.144 mole, of O-benzyl vanillin and 5.2 gm., or 0.088 mole, of potassium cyanide in 100 cc. of ethanol and 20 cc. of water was heated under reflux for 4.5 hours in an atmosphere of hydrogen. At the end of this time the solution was cooled and poured into 400 cc. of ice-cold water. The gum that settled was separated by decantation and dissolved in 400 cc. of ether. This solution was washed with dilute sodium carbonate, dilute sodium bisulfite, and finally with water and dried over anhydrous sodium sulfate. After evaporation of the ether the residual oil was dissolved in 300 cc. of methanol, 150 cc. of acetic acid, and 75 cc. of water and heated under reflux while 39 gm., of zinc dust was added over a

1.5-hour period. The white solid that separated on cooling was recovered with the excess zinc dust, redissolved in acetone and the resulting colorless solution was filtered and poured into a large amount of water. The long, fine, white needles that separated were recovered and dried in vacuo to a weight of 9.5 gm. melting at 141-142°C. Subsequent recrystallization from ethanol failed to raise the melting point. The preparation gave a 28% yield of pure 3,3'-dimethoxy-4,4'-dibenzyloxydesoxybenzoin. Calc. for $C_{28}H_{22}O_3(OMe)_2$: OMe; 13.2%. Found: OMe; 13.0, 13.0%.

Preparation of Desoxybenzoin

The method of Kubiczek (44) for the reduction of veratroin was applied to benzoin. A solution of benzoin (42 gm., 0.20 mole) in 800 cc. of methanol, 400 cc. of glacial acetic acid and 200 cc. of water was heated under reflux on a steam bath while zinc dust (115 gm., 1.74 moles) was added in small portions over a one-hour period. The condenser was set downward for distillation and after 700 cc. of distillate had been collected the residue was chilled and poured into 2 litres of cold water. The yellow solid that separated was recovered, dried and digested with 150 cc. of boiling methanol which was allowed to cool to 35°C. before the undissolved, residual benzoin was removed. Evaporation of the methanol filtrate to about 100 cc. and chilling to -3°C. gave 16 gm., or 41% of theory, of desoxybenzoin melting 54-56°C. The accepted m.p. is 56°C.

Preparation of Desoxyveratroin Oxime (38)

A. A solution of 12 gm., or 0.038 mole of desoxyveratroin and 3.0 gm., or 0.043 mole of hydroxylamine hydrochloride in 30 cc. of pyridine was heated on a steam bath for 5 hours and after cooling was poured into 100 cc. of water. The yellow oil which separated crystallized slowly and the solid was recovered, washed with dilute (25%) methanol and dried in vacuo. The crude yield of 10.5 gm. was recrystallized from 130 cc. of ethanol to give 8.4 gm. (67% of theory) of desoxyveratroin oxime melting at 126-127°C. The accepted melting point is 128°C.

B. A mixture of 12.5 gm. or 0.0395 mole of desoxyveratroin, 15.6 gm., or 0.225 mole of hydroxylamine hydrochloride and 18.8 gm. or 0.028 mole of sodium acetate was stirred in a solution of 940 cc. of ethanol and 170 cc. of water for two days. At the end of this time, the mixture was poured into 3 litres of stirred cold water. The white solid which separated weighed 12.9 gm. and melted at 128.5-129°C. after filtration and air drying. This amount represented a yield of 99% of theory of pure desoxyveratroin oxime. (Calc. for $C_{14}H_8(OCH_3)_4NOH$: OCH_3; 37.5%. Found: OCH_3; 37.3, 37.5%).

Preparation of 3,3'-Dimethoxy-4,4'-dibenzyloxydesoxybenzoin oxime

A. No reaction could be effected when the insoluble 3,3'-dimethoxy-4,4'-dibenzyloxydesoxybenzoin was stirred with hydroxylamine hydrochloride and sodium acetate in 80% ethanol.

B. A solution of 0.33 gm., or 0.00070 mole, of the desoxybenzoin and 0.06 gm., or 0.00086 mole, of hydroxylamine hydrochloride in 10 cc. of pyridine was heated under reflux on a steam bath for 5.5 hours. The clear yellow solution was poured into 100 cc. of water and the white solid that separated was recovered and dried in vacuo. Weight, 0.29 gm (85% of theory) and melting point 136-137°C. Three recrystallizations from ethanol raised the melting point to 137-137.5°C. The melting point was depressed to 124-133°C. on admixture with the starting material.

Reduction of Desoxyveratroin Oxime

A solution of 12.9 gm., or 0.039 mole, of desoxyveratroin oxime in 75 cc. of ethanol and 25 cc. of glacial acetic acid was hydrogenated in a 300 cc. Parr bomb with 3.0 gm. of Raney nickel catalyst and hydrogen at 1300 p.s.i. The heating was adjusted to raise the bomb temperature first to 80°C. in 25 minutes, and then over an additional 50-minute period to 100°C. The bomb was then allowed to cool. Filtration and evaporation of the colorless solution left a clear oil which was partitioned between 90 cc. of 0.3N hydrochloric acid and several extractions with ether. The addition of sodium hydroxide to the aqueous solution precipitated a white solid which was recovered by filtration and dried. The 3,4,3',4'-tetramethoxydesylamine which was thus obtained weighed 8.5 gm., melted at 104.5-105.5°C. and represented a yield of 69% of theory. (Calc. for $C_{18}H_{23}O_4N$: N, 4.41%. Found: N, 4.26%)

Allen and Buck (38) reported the melting point of this compound as 106-107°C.

Preparation of Chloroacetal

The procedure described below was adapted from the work of Natterer (49) on the conversion of chloroacetaldehyde to its acetal.

A 40% aqueous solution of chloroacetaldehyde obtained from the Dow Chemical Co. (530 gm., 2.67 moles) was saturated with ammonium nitrate and ammonium sulfate and extracted with ether. This extract was dried over anhydrous calcium sulfate and the ether was distilled to leave a colorless oil which was dissolved, together with 10 gm. of calcium chloride, in 1600 cc. of absolute ethanol and 600 cc. of absolute benzene. The solution was heated on a steam bath and over the course of 2.5 hours 1600 cc. of distillate was collected while 1000 cc. of ethanol and 300 cc. of benzene were added in increments. The solution was then heated overnight under reflux, 300 cc. of benzene was added and in the succeeding 1.5 hours a further 1300 cc. of distillate was collected. The pot residue after cooling was dissolved in 1500 cc. of ether, the solution extracted several times with water and dried over potassium carbonate followed by magnesium sulfate at 10°C. Fractional distillation of the clear solution gave 120 gm. (30% of theory) of chloroacetal boiling over the range 148-157°C. at 760 mm. The accepted boiling point range of this compound is 154-156°C. at 760 mm.

Preparation of Aminoacetal (55)

A. Each of two 1.6 cm. Carius tubes contained 5.3 gm., 0.035 mole, of chloroacetal, 5.7 gm., 0.05 mole, of ammonium carbonate, 49 cc. of 28% ammonium hydroxide (0.72 mole), 0.43 gm., 0.0025 mole, of potassium iodide and 9 cc. of ethanol. The tubes were sealed and heated in a shaker at 112 to 117°C. for 31 hours. After cooling, the bomb contents were filtered and extracted with ether to remove any unchanged chloroacetal. The aqueous phase was then evaporated in vacuo at 40-50°C. and the heavy oily residue was saturated with potassium carbonate and extracted with ether. The ether extract, after being dried over solid potassium hydroxide and fractionally distilled, gave 3.3 gm. (35%) of aminoacetal boiling over the range 160-165°C. at 760 mm. pressure. Calc. for aminoacetal, $C_2H_5N(OEt)_2$: OEt, 67.6%; neutralization equivalent 133. Found: OEt, 66.9, 66.6%; equivalent weight by titration against 0.030 N hydrochloric acid using a glass electrode, 136. The picrate of this liquid melted from 142-143°C. Both the boiling point of the liquid and the melting point of its picrate were identical with the values quoted in the literature (55) for aminoacetal.

B. In similar preparations employing equivalent amounts of bromoacetal, the yield of aminoacetal always ranged from 11-14% of theory. This yield was also not affected when the run was carried out at 140°C. for 12 hours or at 120°C. for 27 hours.

Condensation of Desoxyveratroin and Aminoacetal

A. A solution of 2.18 gm., 0.0069 mole, of desoxyveratroin and 1.0 cc., 0.0069 mole, of aminoacetal in 50 cc. of ethanol was allowed to stand for 7 days at room temperature. A 100% recovery of the desoxyveratroin was obtained on evaporation of the solvents.

B. A similar solution after being heated under reflux for 30 hours, with a drying tube attached to the condenser, also gave rise to a 100% recovery of desoxyveratroin.

C. When the above trials were repeated with the addition of either 2-3 drops or 5 cc. of glacial acetic acid similar results were obtained.

D. A solution of 2.18 gm., 0.0069 mole, of desoxyveratroin, 1.0 cc., 0.0069 mole, of aminoacetal and one drop of 50% sodium hydroxide in 10 cc. of pyridine was heated under reflux for 18 hours, cooled and precipitated into 50 cc. of water. After mild acidification, the yellow solid that separated was digested with 30 cc. of methanol to leave 0.25 gm. (11%) of veratril. The methanol filtrate from the veratril on evaporation yielded 1.72 gm. (79%) of desoxyveratroin.

E. A solution of 0.8 gm., 0.0026 mole, of desoxyveratroin and 1 cc., 0.0070 mole, of aminoacetal in 6 cc. of dry pyridine was added to 0.5 cc. of dry pyridine saturated with hydrogen chloride. The solution was heated under reflux and in a hydrogen atmosphere for 9 hours and then precipitated into 400 cc. of water to recover 0.57 gm. (71%) of solid desoxyveratroin. Extraction of the aqueous solution with chloroform and evaporation of the extract left a red oil which gave 0.03 gm. (4%) of veratril on treatment with a little ethanol. Finally, the aqueous solution was acidified and extracted with chloroform. A 16% yield (0.15 gm.) of veratric acid resulted from evaporation of the extract.

All products in the above series of reactions were identified by mixed melting point determinations with authentic samples.

F. A mixture of 2.18 gm., 0.0069 mole, of desoxyveratroin and 1 cc. or 0.0069 mole of aminoacetal in a small distillation assembly was heated for 6 hours on a steam bath. During this period, full vacuum was applied to the system and the receiver was placed in a dry ice trap. On cooling, the residual oil was treated with a little water and a 100% recovery of crystalline desoxyveratroin was effected.

G. In a 125 cc. Claisen flask were placed 25 gm. of desoxyveratroin (0.079 mole) and 24 gm. of aminoacetal (0.18 mole). The flask was fitted with a thermometer and a capillary tube supplying nitrogen (both extending into the liquid), a side arm for a condenser and a receiver attached through a 3-way stopcock to either nitrogen or vacuum. Heat was supplied by a conventional GlasCol mantle. After flushing the system with nitrogen, the heating and vacuum were adjusted continuously to give slow but steady distillation with the pot liquid at 150-160°C. The distillation extended over 2 hours after which 19.4 gm. of aminoacetal was added to the residue and the procedure repeated. The addition and distillation of aminoacetal was carried out once more and, after cooling, the residue was treated with a little acetone and filtered. A recovery of 22.6 gm. of pure crystalline desoxyveratroin was obtained in this way.

The red gum obtained by evaporation of the acetone filtrate was treated with Girard's "T" reagent as outlined on page 52 and a further 0.47 gm. of desoxyveratroin was obtained, thereby bringing the total recovery up to 92% of the starting material. The remaining product was 5.0 gm. (or 20% by weight) of an uncrystallized red gum. Chromatography of this gum did not effect a satisfactory purification.

H. A 125 cc. distillation assembly containing 20.0 gm. of desoxyveratroin (0.063 mole) and 33.7 gm. of aminoacetal (0.253 mole) was swept out with nitrogen and the GlasCol heating mantle was adjusted continuously to give slow, uniform distillation of the excess aminoacetal at 760 mm. pressure. The liquid temperature, as read with a thermometer extending to the bottom of the flask, rose steadily over the course of the one-hour distillation from an initial value of 165°C. to 245°C. as the last traces of the excess aminoacetal were carried over. The weight of the distillate was 27.3 gm. while theory called for 25.3 gm. of aminoacetal together with 1.1 gm. of water, or a total of 26.4 gm.

The light yellow still residue was taken up in 100 cc. of ethanol and hydrogenated with 2.0 gm. of Raney nickel in a 300 cc. Parr bomb at 1300 p.s.i. The temperature of the bomb was raised to 80°C. in 20 minutes and then held between 80°C. and 100°C. for an additional 80-minute period. After filtration and evaporation of the bomb contents, the resulting yellow oil was partitioned between 150 cc. of 1 N hydrochloric acid and several extractions with ether.

Neutralization of the acidic aqueous solution with caustic soda gave a mass of white crystals. These crystals were recovered, washed and dried to give 16.5 gm. (or 61% based on desoxyveratroin) of N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal melting from 66 to 68°C. Repeated crystallization from methanol gave fine, white, felted needles and raised the melting point to 69.6-70.0°C. This compound was very soluble in dilute mineral acids, ether, ethyl acetate, chloroform and benzene and only slightly less soluble in ethanol or methanol. Calc. for $C_{24}H_{35}O_6N$: C, 66.47; H, 8.15; N, 3.24; OMe (OEt calculated as OMe) 43.0%. Found: C, 66.52, 66.48; H, 8.26, 8.28; N, 3.25, 3.29; OMe (OEt calculated as OMe) 42.6, 42.2%.

Extraction of the basic aqueous filtrate from the above product with chloroform and evaporation of this extract left 1.4 gm. of an uncrystallizable red gum which was not examined further.

The ether extract from the original acidification with hydrochloric acid was dried over sodium carbonate and evaporated to give 5.9 gm. of a red oil. This oil was taken up in 50 cc. of ethanol and 5 cc. of glacial acetic acid and was heated under reflux for 1.5 hours with 3.2 gm. (0.0188 mole) of Girard's "T" reagent. The resulting red solution was worked up as previously described to give a 1.8 gm. (9%) recovery of pure crystalline desoxyveratroin. At the same time, 4.2 gm. of a Girard neutral red oil was obtained from which 1.8 gm. of a crystalline solid melting from 96-108°C. was separated. Repeated attempts to purify this solid by crystallization techniques failed completely. Since no nitrogen could be detected in a standard analysis, this substance probably consisted of desoxyveratroin reduction products and was not examined further.

I. Subsequent attempts to repeat this condensation with seemingly identical reactants continually led to only 20-25% yields of N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal. The addition of several drops of glacial acetic acid to one reaction mixture did not increase this low yield. When aminoacetal was added over a 2-hour period under the surface of fused desoxyveratroin, stirred and maintained at 245°C. under nitrogen, none of this product could be isolated after hydrogenation.

Reaction of Haloacetals with 3,4,3',4'-Tetramethoxydesylamine

A. A suspension of 3,4,3',4'-tetramethoxydesylamine (2.0 gm., 0.0063 mole) in 5.0 gm. (0.0327 mole) of chloroacetal and 25 cc. of dry xylene was digested under reflux in a nitrogen atmosphere for 21 hours. After the mixture had cooled, the fraction soluble in aqueous acid was separated from the ether-xylene soluble portion. On making the aqueous solution alkaline 0.69 gm., or 35%, of 3,4,3',4'-tetramethoxydesylamine was recovered. Only a heavy black uncrystallized gum was obtained on evaporation of the ether-xylene solution.

B. A solution of 2 gm., 0.0063 mole, of 3,4,3',4'-tetramethoxydesylamine in 75 cc. of dry benzene was treated with 1.61 gm., 0.0082 mole, of bromoacetal (calc. for $C_6H_{13}O_2Br$: Br, 40.6%. Found: Br, 40.4, 40.0%). The solution was allowed to stand at room temperature for 15 hours, after which time 0.38 gm. (19% by weight) of a white amorphous precipitate was separated by filtration. The benzene filtrate was evaporated; the residue was dissolved in dilute hydrochloric acid and this solution was washed with ether and then neutralized with caustic soda to give a 60% recovery of crystalline 3,4,3',4'-tetramethoxydesylamine.

The seemingly amorphous solid was insoluble in all common organic liquids except pyridine, and was also insoluble in water and aqueous acid or alkali. The material was purified by solution in a minimal amount of pyridine followed by precipitation with ether. Three such fractionations followed by several washes with boiling chloroform left the compound with a constant decomposition point of 237.2°C. (heated at 5°C./min.). Found: C, 48.59, 49.07; H, 5.53, 5.66; N, 0.28; OMe, 27.3, 26.4; Halogen 0.0%. No correlation of these data with any one molecular formula could be made.

Ring Closure of the Schiff Base Derived from Desoxyveratroin and Aminoacetal

A. Desoxyveratroin (2.32 gm., 0.0073 mole) and aminoacetal (6.2 cc., 0.0434 mole) were condensed as described on pages 60 and 61.

a) A one-third portion of the crude Schiff base was treated with a solution of 1.5 gm. of phosphorus pentoxide in 6 cc. of concentrated sulfuric acid.

b) Another third was treated with 8 cc. of 80% sulfuric acid and finally,

c) the last third was treated with 6 cc. of concentrated sulfuric acid.

The crimson solutions were allowed to stand at room temperature for 40 hours, after which each was mixed with 30 gm. of chopped ice to give a chestnut brown precipitate. The aqueous slurries were then made alkaline with caustic soda and the organic bases were extracted with benzene. Extraction of the benzene solutions with 250 cc. of 0.10 N hydrochloric acid and addition of excess caustic soda to the extracts gave a slightly brown solid in each case:

a) 0.32 gm. melting 141-146°C.,

b) 0.52 gm. melting 137-144°C.,

c) 0.39 gm. melting 140-145°C.

These three products, shown to be identical by mixed melting point determinations, were combined and decolorized with charcoal in 50 cc. of hot ethanol. On cooling the filtered ethanol solution, 0.49 gm. of yellow needles melting at 164 to 165°C. were obtained, representing a yield of 19.8% (based on $C_{20}H_{21}O_4N$). Three subsequent recrystallizations raised the melting point to 164.5-165.5°C. Calc. for $C_{20}H_{21}O_4N$: C, 70.75; H, 6.25; N, 4.13; OMe, 36.6%; Mol. wt., 339. Found: C, 70.51, 70.78; H, 6.33, 6.25; N, 4.01, 4.02; OMe, 35.9, 36.1%; Mol. wt. determined cryoscopically in benzene, 354, 336. Determinations made in anisole by the Zerewitinoff method (57) showed the presence of 0.12 and 0.07 gm. of active hydrogen per mole.

The compound was insoluble in water and ether, very soluble in chloroform, pyridine, glacial and aqueous acetic acid, and sparingly soluble in acetone, methanol and ethanol. Treatment of an acetone solution of this compound with a little concentrated hydrochloric acid precipitated the orange colored hydrochloride of the base. This hydrochloride was only sparingly water-soluble, was rather unstable on recrystallization from hot solvents and melted with decomposition at 212°C. Calc. for $C_{20}H_{21}O_4N \cdot HCl$: Cl, 9.46%. Found: Cl, 9.36, 9.33%.

B. Desoxyveratroin (25 gm., 0.079 mole) and aminoacetal

(30 gm., 0.225 mole) were condensed as described on pages 60 and 61 to give 29.8 gm. of the crude Schiff base. Hydrogenation of 14.8 gm. of this oil yielded 3.82 gm. of crystalline N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal, or 22.5% based on the desoxyveratroin.

The remaining 15.0 gm. of the crude Schiff base was stirred with 160 cc. of 83% sulfuric acid for 20 hours, after which time the mixture was worked up as described in Section A to yield 2.89 gm. (or 21.5%) of the yellow crystalline base, $C_{20}H_{21}O_4N$. The brown ethanol filtrate from the recrystallization of this base was evaporated to dryness and the brown residual powder was digested exhaustively with boiling (50-80°C.) petroleum ether. Filtration and evaporation of the clear yellow extract left 0.39 gm. of a yellow-white solid melting over the range 134-138°C. This solid was dissolved in benzene which had been dried over anhydrous calcium chloride and the solution was run onto an alumina column. The yellow base, $C_{20}H_{21}O_4N$, was washed through the column under these conditions and a further 0.17 gm. of this base, melting at 163-165°C., was obtained on evaporation of the benzene. The alumina column next was extruded and all but the upper 0.5 cm., which was a deep brown color, was extracted with 5% pyridine in methanol. This extract, on filtration and evaporation, yielded 0.15 gm. (or 1.1%) of papaverine melting over the range 146.5-147.5°C. Calc. for $C_{16}H_9(OMe)_4N$: OMe, 36.6%. Found: OMe, 36.3, 36.0%. The base was converted to its hydrochloride, which melted at 221-222°C.

Calc. for $C_{20}H_{21}O_4N\cdot HCl$: Cl, 9.46%. Found: Cl, 9.38, 9.25%. The melting points of the base and its hydrochloride were identical with those of authentic papaverine and its hydrochloride respectively, and no depression in the melting point was observed on admixture of the appropriate compounds.

C. A similar reaction, in which the crude Schiff base was treated with 83% sulfuric acid and four aliquots were isolated by pouring onto ice after 15, 20, 27 and 40 hours respectively, gave rise in each case to 18 to 20% yields of the yellow base, $C_{20}H_{21}O_4N$.

D. The attempts outlined below were made to obtain positive chemical evidence for the structure of the yellow base, $C_{20}H_{21}O_4N$.

A 95% recovery of the base was effected after it had been heated under reflux in benzene with excess methyl iodide for 3 hours; a 98% recovery from acetic anhydride in pyridine at room temperature for 3 days; a 100% recovery from benzoyl chloride shaken with excess aqueous alkali; and complete destruction of the compound in acetic anhydride, catalyzed with ferric chloride, for 5 hours at 100°C. All these negative experiments pointed to the absence of the N-H group.

The base was completely destroyed when treated with zinc dust and hydrochloric acid at 30 to 40°C. for 25 minutes. However, reduction with Raney nickel and hydrogen in ethanol at 1600 psi and 130-140°C. for 1 hour proceeded quantitatively. A

95% yield by weight of a clear, colorless, acid soluble oil was obtained which did not exhibit the characteristic orange-yellow color of the original base when treated with hydrochloric acid. None of the usual amine salts of this product could be obtained in a crystalline form, but when a portion of the oil was shaken with excess benzenesulfonyl chloride and aqueous alkali a colorless, insoluble gum was obtained which did not redissolve in dilute hydrochloric acid. This gum was not further investigated.

Oxidation of the base with neutral or slightly basic potassium permanganate in aqueous acetone gave only a relatively low yield of veratric acid.

Attempted Ring Closure of the Schiff Base Derived from Desoxybenzoin and Aminoacetal

A solution of 4.5 gm. (0.023 mole) of desoxybenzoin in 14.5 gm. (0.11 mole) of aminoacetal was placed under nitrogen in a 25 cc. distillation assembly. A GlasCol mantle supplied heat for a slow distillation of the excess aminoacetal and the water formed during the condensation. After 2.5 hours a distillate of 11.6 gm. was collected whereas theory would demand 11.5 gm. of aminoacetal plus 0.4 gm. of water. The red oily residue, 6.0 gm., in the Claisen flask was taken up in ether, washed with a little aqueous sodium bicarbonate and dried over anhydrous sodium carbonate.

After evaporation of the ether, the red oil was frozen in solid carbon dioxide - acetone and was treated with 35 cc. of cold, concentrated sulfuric acid. The resulting deep brown solution was allowed to stand at room temperature for 30 hours, after which time it was poured onto 300 gm. of chopped ice. The brown amorphous solid that separated was stirred with dilute alkali until the washings gave a negative test for sulfate ion. After being dried, the product was insoluble in ethanol, chloroform, acetone and dilute mineral acids but dissolved in glacial acetic acid. Attempted fractionation and crystallization completely failed to alter the brown amorphous nature of this material.

Ring Closure of the Hydrogenated Schiff Base Derived from Desoxyveratroin and Aminoacetal (See Tables II to IV)

A. Six 0.20 gm. (0.00046 mole) portions of the pure hydrogenated Schiff base, N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI) previously prepared were dissolved in chilled solutions of 83, 75, 65, 50, 35 and 20% sulfuric acid by weight.

After 17 hours at room temperature the solutions ranged from a deep brown in the more concentrated acids to colorless in the 20% acid. At this time all were poured into ice water and the resulting solutions were extracted with benzene. In all cases evaporation of the benzene left 20-30 mg. of a yellow gum that was obviously insoluble in aqueous alkali or acid. This gum was not examined further. When the original sulfuric acid solutions were made alkaline, no precipitates appeared except one of 10 mg. m.p. 149-151°C., from the condensation with 75% sulfuric acid, and another, 30 mg. from the experiment with 20% acid. The first precipitate proved to be 6.4% of the crystalline compound $C_{20}H_{23}O_4N$ discussed below, while the second represented 15% of unchanged starting material.

B. A solution of 0.10 gm. or 0.00023 mole of the hydrogenated Schiff base (XLVI) in 5.00 cc. of concentrated hydrochloric acid was allowed to stand at room temperature. After various periods of time a 1 cc. aliquot was removed, poured onto ice, made alkaline with caustic soda and filtered. The gummy precipitates that were collected all exhibited a negative dinitrophenylhydrazine test for the free carbonyl function. They were not examined further.

The five filtrates were then added separately to a distillation assembly and any free ethanol was distilled and collected in a receiver cooled at -60°C. The distillates (each about 7 cc.) were then treated with 2.5 gm. of phenol and 10 cc. of constant boiling hydriodic acid in the usual methoxyl distillation assembly and the free ethanol was estimated. When the procedure had been standardized with very dilute aqueous solutions of known ethanol content, it was found that hydrolysis of the hydrogenated Schiff base for 0.5, 3, 6, 24 and 51 hours gave rise respectively to 14, 71, 98, 100 and 99% of the theoretical amount of ethanol.

C. A solution of 0.200 gm. of N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal (XLVI) in 10 cc. of 2 N hydrochloric acid was heated under reflux for 7 hours, when the liberation of ethanol was found to be 92% complete. In this case, the gummy yellow solid that was isolated exhibited a very strong positive dinitrophenylhydrazine test for the free carbonyl function. The yield amounted to 0.138 gm. or 84%. This material was treated with 2 cc. of 83% sulfuric acid at room temperature for 4 hours. The brown solution was then poured onto ice, washed with benzene, filtered, and made alkaline to precipitate a white solid. This solid, after being dried, melted at 148-151°C., and the 0.050 gm. yield represented 38% based on the free aldehyde. The solid was the crystalline compound $C_{20}H_{23}O_4N$ discussed below.

D. One gram (0.0044 mole) of arsenic pentoxide was stirred for 0.5 hour in 17 cc. of hot 83% sulfuric acid. After chilling the mixture, 1.0 gm. of the hydrogenated Schiff base (0.00231 mole) was added and the solution was allowed to stand at room temperature for 4.5 hours with occasional shaking. The solution was then worked up as before to yield 0.19 gm. (or 25% of theory) of a white solid soluble in hydrochloric acid and melting at 149-152°C.

E. A mixture of 1.5 gm. (0.00346 mole) of the hydrogenated Schiff base, 2 gm. (0.0087 mole) of arsenic pentoxide and 17 cc. of 83% sulfuric acid was stirred for 6 hours at room temperature. This time, 0.56 gm. (or 48% of theory) of a white solid melting at 152-153°C. was obtained on working up the mixture as described before.

F. Six solutions of 1.0 gm. (0.00231 mole) of the hydrogenated Schiff base in 11 cc. of 83% sulfuric acid were allowed to stand at room temperature for 5, 6, 7, 8, 10 and 13 hours. After working up as already described, the acid-soluble white solids melting at 150-154°C. amounted to 34, 42, 56, 54, 18, and 2% of theory, based on $C_{20}H_{23}O_4N$, respectively.

With 0.40 gm. (0.00092 mole) of the hydrogenated Schiff base in 6 cc. of 75% sulfuric acid for 4, 6, 8, and 11 hours the yields of this solid, $C_{20}H_{23}O_4N$, were 1.6, 6.8, 30, and 12% respectively.

When the basic white solid, obtained as a product in these reactions, was treated with 83% sulfuric acid at room temperature, the solid recovered by the usual procedure after 2 and 18 hours amounted to 48 and 14% respectively.

G. The white, basic solids melting over the range 149-154°C. obtained in experiments A, C, D, E, and F were all found to be identical and several recrystallizations by solution in acid and precipitation from alkali raised the melting point to 155.5-156°C. Calc. for $C_{20}H_{23}O_4N$; C, 70.34; H, 6.80; N, 4.10; OMe, 36.4%. Found: C, 70.28, 70.25; H, 6.88, 6.81; N, 4.05, 4.11, 4.02; OMe, 35.7, 35.5%.

Treatment of this solid, $C_{20}H_{23}O_4N$, with acetic anhydride in pyridine for 3 days at room temperature gave a 94% yield of the acetyl derivative melting at 203.5-203.8°C. Calc. for $C_{22}H_{25}O_5N$: N, 3.66%; OMe, 32.4%. Found: N, 3.56, 3.60%;

OMe, 32.1, 32.3%.

Attempts to dehydrogenate the original compound, $C_{20}H_{23}O_4N$, with selenium at 250°C. under nitrogen, with palladium on charcoal at 190°C. and with palladium black in boiling decalin led only to its complete destruction.

Attempted Conversion of the Hydrogenated Schiff Base to the Corresponding Free Aldehyde via Its Thioacetal

To a stirred suspension of 15 cc. of ethyl mercaptan (0.20 mole) in 100 cc. of concentrated hydrochloric acid at room temperature was added 3.65 gm. or 0.0084 mole of the crystalline hydrogenated Schiff base. After 24 hours the mixture was drowned into 100 cc. of water and the solution was washed with benzene. The white gum that was precipitated when the solution was made alkaline with caustic soda was extracted with benzene. After drying over anhydrous sodium sulfate, the benzene extract, on evaporation, yielded 1.98 gm. of a colorless oil. This oil was dissolved in acetone and treated with a few drops of concentrated hydrochloric acid. The heavy gum, left on evaporation of the solution, slowly crystallized while it was heated in a water bath at 60°C. *in vacuo* for 2 hours. The white solid was transferred to a filter and washed with dry acetone followed by dry ether. Weight, 1.59 gm., and melting point 184-187°C. (heated at 12°C./min.). This product was recrystallized by solution in a little methanol followed by precipitation into dry ether. Weight, 1.38 gm. and melting point 184-185°C. (heated at 6°C./min.). Found: C, 60.03; H, 5.87; N, 3.08, 2.99; S, 6.90, 7.08; OMe, 28.0, 27.9%. No correlation of these data with a reasonable molecular structure could be made. When the purified hydrochloride was treated with alkali to liberate the free base only an oil, which appeared to decompose, could be obtained.

A solution of 1.29 gm. of the crystalline hydrochloride in water, was precipitated with alkali and extracted with benzene. The colorless oil left after evaporation of the dried extract was dissolved in 70 cc. of acetone to which had been added 3.75 gm. of mercuric chloride, 4.8 gm. of cadmium carbonate, and 1.0 cc. of water. The mixture was stirred at room temperature for 24 hours after which time it was filtered. The residue left after evaporation of the filtrate was dissolved in a large volume of chloroform and washed with dilute aqueous potassium iodide followed by water. Evaporation of the dried chloroform solution left 1.17 gm. of a brilliant yellow solid melting with decomposition at 85°C. Repeated purification of this solid by solution in acetone and precipitation with ether raised the melting point to 109°C. Found: N, 1.88, 1.90; OMe, 16.9, 17.2; Hg, 13.8%. No reasonable structure can be correlated with these data.

A solution of 0.800 gm. of this mercury complex in aqueous acetone containing a few drops of acetic acid was treated with hydrogen sulfide until no further precipitation of black mercuric sulfide occurred. This precipitate was filtered, dried and weighed to yield the analytical figure for mercury quoted above. The filtrate was made alkaline after dilution with water and extracted with benzene. Evaporation of the dried extract left 0.468 gm. of a colorless oil which was negative to tests for halogen and carbonyl groups.

This oil was treated with 5 cc. of 83% sulfuric acid at room temperature. Five identical aliquots were removed at various times and the yield of $C_{20}H_{23}O_4N$ was determined as outlined before. After 1.5, 3, 5, 7 and 15 hours, the yields of $C_{20}H_{23}O_4N$ were 22, 30, 34, 19, and 2% respectively. The authenticity of these products was ascertained by melting point determinations made on admixture with samples of $C_{20}H_{23}O_4N$.

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

Veratroin, prepared by the condensation of veratric aldehyde in presence of potassium cyanide, was reduced to desoxyveratroin by zinc dust in acetic acid. It was necessary to purify the compound from veratril by condensation with Girard's "T" reagent for isolated carbonyl groups and, after recovery, the over-all yield was only 18%. In a similar way the benzoin prepared from o-benzyl vanillin was reduced to give a 28% yield of the new compound 3,3'-dimethoxy-4,4'-dibenzyloxydesoxybenzoin (m.p. 141-142°C. and oxime m.p. 137-137.5°C.). The preparation of desoxyveratroin oxime was improved to the point where a quantitative yield was obtained under very mild conditions. High pressure hydrogenation at 80° to 100°C. and over a Raney nickel catalyst reduced this oxime in 70% yield to the known 3,4,3',4'-tetramethoxydesylamine.

The preparation of chloroacetal from chloroacetaldehyde, with ethanol in presence of a calcium chloride catalyst, was improved by the continual removal of the water of condensation by azeotropic distillation with benzene. The conversion of chloroacetal to aminoacetal by heating under pressure with aqueous ammonia - ammonium carbonate gave yields of 30 to 35% comparable with those reported in the literature. Bromoacetal, under the same conditions only gave an 11-14% yield. It was found that increasing the temperature to 140°C. or the reaction time at 115-120°C. did not markedly increase this low yield.

Desoxyveratroin and aminoacetal could not be condensed together under any of the conditions tried, unless the temperature was at least 165°C. At a temperature of approximately 200° and in a nitrogen atmosphere, variable yields of 30-85% of the Schiff base were obtained. The Schiff base was completely destroyed when heated at 245°C. for prolonged periods. This compound was hydrogenated in ethanol over Raney nickel at 1300 p.s.i. and 80-100°C. to give 20-61% of crystalline N-(3,4,3',4'-tetramethoxydesyl)-aminoacetal, m.p. 70°C. Other investigators have failed to prepare this compound.

Treatment of the Schiff base of desoxyveratroin and aminoacetal with concentrated sulfuric acid, 83% sulfuric acid, or concentrated sulfuric acid - phosphorus pentoxide mixtures, produced an 18 to 22% yield of a new compound supposed to be 2,3,-di-(3,4-dimethoxyphenyl)-5-pyrrolenine, melting at 165°C., as well as a 1.1% yield of papaverine. The former compound would arise by ring closure of the aldehyde group of the acetal unit to the active methylene group, while papaverine would result from closure to the veratryl nucleus. Attempts to form the corresponding Schiff base of desoxybenzoin and aminoacetal, and to bring about a subsequent ring closure, gave only an amorphous substance.

Ring closure of the crystalline hydrogenated Schiff base of desoxyveratroin and aminoacetal in sulfuric acid of varying concentrations produced up to 56% of a new compound melting at 156°C. and analyzing for dihydropapaverine. By analogy with the above pyrrole formulation, this compound was believed to be 2,3,-di(3,4,-dimethoxyphenyl)-Δ^3-pyrroline. A somewhat extensive study of the reaction conditions suggested that 20 to 65% sulfuric acid hydrolyzed the acetal but failed to bring about ring closure of the resulting aldehyde. Sulfuric acid of 83% concentration gave the best results, although the product was not entirely stable in this reagent.

The reaction of bromoacetal with 3,4,3',4'-tetramethoxydesylamine in benzene at room temperature gave rise to a 20% yield of a compound decomposing at 237°C. No structure could be proposed for this compound.

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